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Concordance in parent and offspring cortico-basal ganglia white matter connectivity varies by parental history of major depressive disorder and early parental care

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Abstract

Social behavior is transmitted cross-generationally through coordinated behavior within attachment bonds. Parental depression and poor parental care are major risks for disruptions of such coordination and are associated with offspring's psychopathology and interpersonal dysfunction. Given the key role of the cortico-basal ganglia (CBG) circuits in social communication, we examined similarities (concordance) of parent–offspring CBG white matter (WM) connections and how parental history of major depressive disorder (MDD) and early parental care moderate these similarities. We imaged 44 parent–offspring dyads and investigated WM connections between basal-ganglia seeds and selected regions in temporal cortex using diffusion tensor imaging (DTI) tractography. We found significant concordance in parent–offspring strength of CBG WM connections, moderated by parental lifetime-MDD and care. The results showed diminished neural concordance among dyads with a depressed parent and that better parental care predicted greater concordance, which also provided a protective buffer against attenuated concordance among dyads with a depressed parent. Our findings provide the first neurobiological evidence of concordance between parents-offspring in WM tracts and that concordance is diminished in families where parents have lifetime-MDD. This disruption may be a risk factor for intergenerational transmission of psychopathology. Findings emphasize the long-term role of early caregiving in shaping the neural concordance among at-risk and affected dyads.

Key words: concordance; parent–offspring bonding; major depression; DTI; social cognition

Introduction

Humans are social by nature and biologically prepared to connect with others to promote their survival (Bowlby, 1969; Hardy, 2009). The parent–offspring bond, the first and most significant social relationship throughout life, is the context of offspring physical, social-emotional and cognitive growth (Sroufe, 1988). Therefore, offspring who experience chronic familial stressors, such as parental depression and/or poor parental care, are vulnerable to a myriad of adverse outcomes throughout life, including depression and other psychiatric illnesses, as well as social difficulties such as socio-cognitive deficits and behavioral problems (Cummings et al., 2005; Weissman et al., 2016; Weissman, 2020).

As mammals, our brain develops through the process of 'biobehavioral synchrony', the on-going exchanges of behavioral, hormonal and physiological signals between parent and offspring during social contact (Feldman, 2012). In humans, concordance in parent–offspring physiological processes is based not only on proximity and touch, as seen in other mammals (Curley and Champagne, 2016), but also on shared empathic experiences, social understanding and perspective-taking, and has been suggested as a potential mechanism underlying human social bonding (Creaven et al., 2014; Ebisch et al., 2012; Feldman et al., 2010, 2011; Mayo and Gordon, 2020; van Bakel and Riksen-Walraven, 2008).

Parent–offspring concordance of social cues and physiological processes (e.g. hormones, heart rhythms, respiratory sinus arrhythmia) during childhood and adolescence provides critical inputs to offspring optimal neurobehavioral development. Parent–offspring concordance supports offspring's participation in social life, including development of self-regulation, empathy and symbolic skills in early childhood, and pro-sociality and social cognition later in life, which in turn support the ability to form and maintain social relationships and to parent the next generation (Abraham et al., 2014, 2016; Feldman, 2012, 2017). Studies in animals (Perkeybile and Bales, 2017) and humans (Abraham et al., 2017; Feldman, 2017) have shown that intergenerational transmission of social behavior is modulated by early parental care and regulated by the cortico-basal ganglia (CBG) circuits during moments of interpersonal synchrony (Schirmer et al., 2016).

The human basal ganglia, including the caudate, putamen, nucleus accumbens (NAcc) and pallidum, is a central node of the subcortical dopaminergic motivation/reward circuitry that supports affective representation of others and multiple social goals by integrating reward-related learning, motivation, motor control and habit formation (Delgado, 2007; Báez-Mendoza and Schultz, 2013). Its connections with cortical regions involved in empathy, simulation and theory-of-mind (ToM), are translated into higher-order social behavior by providing incentive for long-term social goals (Shamay-Tsoory, 2011; Gordon et al., 2013; Van Den Bos et al., 2015), and by using reward outcomes to guide social cognition and form stable attachments, including parent–offspring bonding, pair-bonding and friendships (Rilling and Young, 2014; Tops et al., 2014). Two systems in the mesocorticolimbic pathway—dopamine (DA) and oxytocin (OT) form tighter crosstalk during periods of bond formation, including the parent–offspring bonding, to reorganize neurobiological systems implicated in emotion, reward and motivation processes around social experiences (Feldman, 2017; Ulmer-Yaniv et al., 2016). The CBG circuit holds particular importance in the context of parental depression since its development is sensitive to early experiences within child-rearing contexts, as well as

its central role in underpinning maternal and paternal care, and in co-wiring of parent's and offspring's brains and behavior into a synchronous unit that supports the offspring's brain development (Skelin et al., 2015; Nusslock and Miller, 2016; Qu et al., 2016; Feldman, 2017). Also, aberrant functionality and connectivity of CBG circuits along with deficits in multiple social cognitive domains were found to be associated with depression (Marchand et al., 2012; Ma et al., 2012; Gabbay et al., 2013).

While parent–offspring concordance has been demonstrated on behavioral, arousal and hormonal levels, much less is known about how two brains coordinate in the context of social bonding, and how neural concordance varies by risk factors such as parental depression and poor parental care. Recently, neuroimaging research in healthy population has pinpointed dyadic neural concordance in the basal ganglia (Stephens et al., 2010), and mainly in temporal cortical structures implicated in social communication, including the fusiform gyrus (FG)/inferior temporal gyrus (ITG), superior temporal sulcus (STS) and temporoparietal junction (TPJ). This neural concordance was associated with degree of social connectedness and the quality of relationship, such as cooperation and its success, and with greater shared intentionality between partners (e.g. Atzil et al., 2012; Cui et al., 2012; Goldstein et al., 2018; Hasson, 2004; Kinreich et al., 2017; Levy et al., 2017; Meyer et al., 2019; Miller et al., 2019; Mu et al., 2016; Stephens et al., 2010; Tang et al., 2016). Only two studies measured concordance in neural structure and activity in at-risk sample of dyads with a depressed mother and found that depressed mothers' cortical thinning in middle temporal gyrus (MTG; Foland-Ross et al., 2016) and activation of the putamen (Colich et al., 2017) predicted their never-depressed daughters' cortical thinning and activation in the same areas, respectively. No studies which we are aware of have examined dyadic concordance in parents and offspring CBG white matter (WM) connectivity and how such concordance varies by parental major depressive disorder (MDD) status and early parental care.

Given the role of aberrant social-cognitive processing in the profound and pervasive social impairments displayed by individuals with MDD (Tse and Bond, 2004), we examined dyadic concordance in parents and offspring CBG WM connectivity in 44 dyads from a sample of three generations of families followed prospectively up to 40 years (Weissman et al., 2016), comprising parents (second generation) with and without a lifetime history of major depression disorder (MDD) and their depressed and never-depressed offspring (third generation). We used diffusion tensor imaging (DTI) tractography to examine parent–offspring concordance of the integrity of WM tracts, which connect the basal ganglia nuclei with six temporal regions, all of which implicate in mental representation of others, social communication and parent–offspring bonding. Regions were selected based on recent social neuroscience literature on social cognition and brain coupling (for review see: Van Overwalle, 2009; Shamay-Tsoory, 2011; Adolfi et al., 2017; Long et al., 2020) (Figure 1).

To assess concordance between parents and offspring, we examined the similarities (as indicated by positive correlations) of parent and offspring CBG connections. We hypothesized that CBG connection strength would correlate in parent and offspring above and beyond parent MDD status (Hypothesis 1). Second, we investigated whether and how parent-level risk factors for psychopathology and social cognition impairments—parent lifetime-MDD and low parental care—would moderate these associations. Based on previous work demonstrating that parental depression is associated with attenuated dyadic behavioral (Field et al., 1990; Murray and Cooper, 1996; Tronick
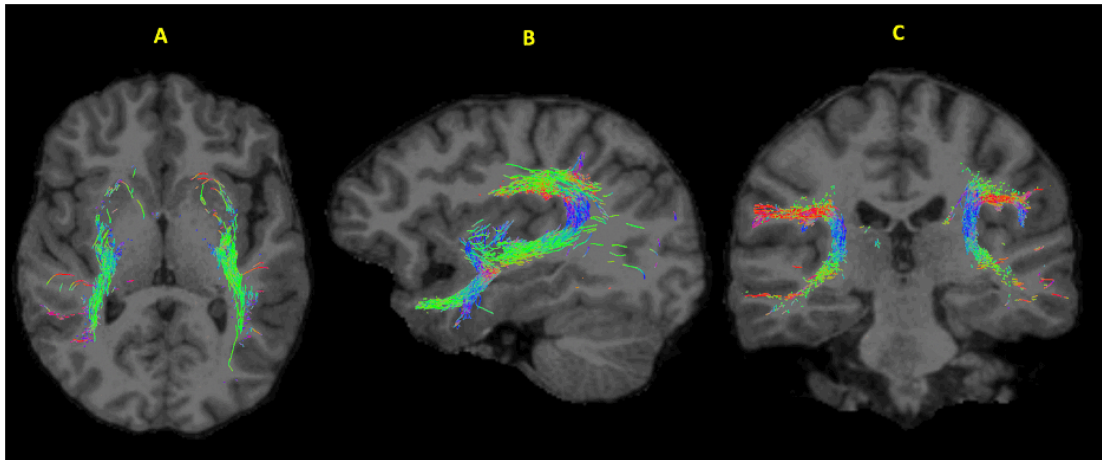
Fig. 1. Cortico-basal ganglia white matter connectivity.

Illustration of the white matter fiber tracks connecting the basal ganglia with the temporal regions of interest. A, axial; B, coronal; C, sagittal views.

and Reck, 2009; Granat *et al.*, 2017), hormonal (Merwin *et al.*, 2017), and autonomic physiology (Woody *et al.*, 2016) coordination, we hypothesized that parental lifetime-MDD would be associated with reduced or diminished parent–offspring neural concordance (Hypothesis 2). We assessed early parental care using the Parental Bonding Instrument (PBI), which is an instrument to measure parent–child bonding during the first 16 years of life (Parker *et al.*, 1979) on the parental Care dimension (sensitive and responsive parenting). Given evidence that individual differences in quality of early parent–offspring relationship play an important role in physiological concordance (Atzil *et al.*, 2012; Smith *et al.*, 2016; Suveg *et al.*, 2019), we hypothesized that higher levels of parental Care during childhood, as reported by offspring, would be associated with a greater parent–offspring concordance of CBG WM connections (Hypothesis 3). Finally, since social attachments act as a protective buffer against many negative consequences of stress and adversity, including parental depression (Hagan *et al.*, 2011; McNeal *et al.*, 2017), and not all depressed parents necessarily display poor parental care (Flykt *et al.*, 2010), we sought to determine if higher levels of parental Care can protect the attenuated dyadic concordance from the effects of parental lifetime-MDD (Hypothesis 4).

Materials and methods

Participants

The study began in 1982, with recruitment of adults (probands, generation one, G1) with moderate to severe MDD seeking treatment at outpatient facilities; and a comparison group of adults from the same community with no lifetime psychopathology, as determined by several interviews. The G1 probands, as well as their children (G2) followed over up to six assessment waves, corresponding to year 0 (Baseline), 2, 10, 20, 25, and 30. G3 (grandchildren) aged into the study starting time 10 or 20. G2/G3 offspring of the probands with MDD constituted the high-risk for depression group, and those of probands without psychopathology, the low risk group. Complete details on study design, sample selection, and assessments are reported elsewhere (Weissman *et al.*, 2016). This study is based on year 30 of the study, at

which time the magnetic resonance imaging (MRI)/DTI assessment was completed. The Institutional Review Board of the New York State Psychiatric Institute (NYSPI) approved the study procedures. Adult participants provided informed consent; minors provided informed assent, and a parent/guardian provided consent. A total of 66 participants, consisting of 27 (16 mothers) G2 parents aged 39–59 years and their 39 (19 daughters) biological G3 offspring aged 10 to 31 years, were included. These G2 and G3 participants were distributed into 44 biological parent–offspring dyads, consisting of 24 dyads with parents diagnosed with Lifetime-MDD, and 20 dyads with never-MDD parents (Table 1). All participants were Caucasian, and G1 participants were all drawn from the same community. Exclusion criteria consisted of psychotic symptoms, pregnancy and MRI contraindications.

MRI and DTI data

Structural MRI (voxel $= 1$ m^3, dimensions $= 256 \times 256 \times 162$) and diffusion MRI (voxel $= 0.94 \times 0.94 \times 2.5$ mm^3, dimensions $= 256 \times 256 \times 58$, b $= 1000$ sm^{-2}, direction $= 15$) scans were acquired on a GE 3T scanner. Cortical and subcortical parcellations of the structural MRI scans were performed with Freesurfer (http://freesurfer.net), and these parcellations were used for individualized seed and target regions for tractography, as described below.

To quantify the number of streamline counts, an index of structural connectivity, diffusion MRI scans were processed with MRtrix (https://www.mrtrix.org/; Tournier *et al.*, 2019). Briefly, with this approach, diffusion MRI scans are first denoised using random matrix theory allowing for a data-driven threshold for Principal Component Analysis denoising (Veraart *et al.*, 2016). This denoising method enhances quantitative and statistical interpretation (Veraart *et al.*, 2016). Denoised images then undergo eddy current and motion correction, brain extraction from three non-diffusion-weighted images (taking their median), and bias field correction using an N4 algorithm (N4ITK) in Advanced Normalization Tools (ANTs) (Andersson and Sotiropoulos, 2016; Tustison *et al.*, 2010). Fiber orientation distributions are then estimated from the preprocessed diffusion MRI scans and probabilistic tractography is performed

Table 1. Characteristics of study parents and offspring

	Total sample	MDD parent—Never-MDD offspring dyads (numbers, %)	MDD parent-MDD offspring dyads (numbers, %)	Never-MDD parent-MDD offspring dyads (numbers, %)	Never-MDD parent—Never-MDD offspring dyads (numbers, %)	Test statistic	P-value
Number of dyads	44	17 (38.6%)	7 (15.9%)	6 (13.6%)	14 (31.8%)		
Number of participants:	66	**Lifetime-MDD**		**Never-MDD**			
Second generation (G2)—parents	27	16 (59%)		11 (41%)			
Third generation (G3)—offspring	39	10 (25.6%)		29 (74.4%)			
Age (years):							
Second generation (G2)	Mean ± SE: 48.20 ± 0.68 Range: 38.9–59.6	47.1 ± 0.82	49.6 ± 2.3	47.8 ± 1.77	48.9 ± 1.37	$F_{(3,41)} = 0.642$	0.593
Third generation (G3)	Mean ± SE: 20.28 ± 0.71 Range: 10.7–31.4	19.04 ± 0.82	20.9 ± 1.975	21.9 ± 2.24	20.7 ± 1.53	$F_{(3,41)} = 0.712$	0.551
Parent (G2)-offspring (G3) age interval	Mean ± SE: 27.9 ± 0.65 Range: 19.20–38.30	28.30 ± 0.08	28.83 ± 0.45	25.82 ± 0.59	28.4 ± 0.06	$F_{(3,41)} = 1.326$	0.256
Gender:							
Second generation (G2) participants/dyads							
Male	Participants: 11 (40.7%) Dyads: 21 (47.7%)	9 (52.9%)	3 (42.9%)	5 (83.3%)	4 (28.6%)	$X^2 = 5.36$	0.147
Female	Participants: 16 (59.3%) Dyads: 23 (52.3%)	8 (47.1%)	4 (57.1%)	1 (16.7%)	10 (71.4%)		
Third generation (G3) Participants/dyads							
Male	Participants: 20 (51.3%) Dyads: 21 (47.7)	8 (47.1%)	2 (28.6%)	5 (83.3%)	6 (42.9%)	$X^2 = 4.21$	0.239
Female	Participants: 19 (48.7%) Dyads: 23 (52.3%)	9 (52.9%)	5 (71.4%)	1 (16.7%)	8 (57.1%)		

Values are mean ± SE unless specified.

based on second-order integration over fiber orientation distributions (iFOD2) with a target streamline count of 10 million (Tournier *et al.*, 2019). Tractograms are filtered using spherical-deconvolution informed filtering of tractograms (SIFT) with a streamline count target of 1 million. SIFT permits mapping of the streamline estimation to an individual's diffusion MRI scan in addition to updating the streamline reconstruction to improve model fit. Finally, connectivity matrices were generated for each participant using the brain parcellation and segmentation obtained from the structural MRI scan from the same person. In this way, the structural connectome estimates reflect individualized connectomes constrained by the individual's neuroanatomy. A prior macaque study suggests the validity of streamline counts as an indicator of fiber connection strength with the number of streamlines significantly correlating with tract-tracing strength in the macaque brain (van der Heuvel *et al.*, 2015).

The following steps were taken to address potential effects of head motion during MRI scanning. First, the diffusion weighted scans were manually inspected volume by volume by a trained technician prior to any processing. No volumes with motion or other imaging artifacts were identified during manual inspection, and thus, all volumes were used for analysis. Second, rotational and translational head motion parameters were calculated for each scan. We ran independent sample t-tests and no statistically significant differences average rotation and average translations were found between high *vs* low risk and lifetime-MDD *vs* no MDD and high *vs* low parental Care ($P > 0.05$; see Supplementary information Table S1). Head motion was minimal (average rotation < 0.01 mm and average translation < 0.6 mm).

Region of interest (ROI) included four basal-ganglia seed regions: the NAcc, caudate, putamen and pallidum, and six cortical regions within the temporal lobe. We chose to focus on regions within the temporal lobe due to their important role in social cognitive processing (Van Overwalle, 2009), and the fact that these regions support brain-to-brain neural synchrony (Dikker *et al.*, 2014; Jiang *et al.*, 2012; Liu *et al.*, 2017; Tang *et al.*, 2016). All six temporal regions, including the STS, MTG, ITG, FG, TPJ and temporal pole (TP) (Figure 1) were commonly found in ToM, empathy, brain coupling and social communication paradigms.

The schedule for affective disorders and schizophrenia

At each wave, MDD was diagnosed using the Schedule for Affective Disorders and Schizophrenia-Lifetime Version; the adult version for participants over age 18 years (Mannuzza *et al.*, 1986) and the child version for participants 6 to 17 years of age modified for DSM-IV for children and adolescents (Kaufman *et al.*, 1997). Each family member was interviewed independently and blinded to the clinical status of other family members, by trained doctoral- and masters-level mental health professionals (reliability, which was high, has been documented elsewhere (Weissman *et al.*, 2016). Final diagnoses were made by an experienced (Ph.D. or M.D. clinician) using the best estimate procedure (Leckman, 1982).

Parent–offspring bonding

Parental Care was measured by the PBI, a widely used, validated and reliable measure of parent-child bonding (Parker *et al.*, 1979; Parker, 1990) at time 30. The PBI has survived many tests and

years and remains an important clinical moderator of outcomes in intergenerational research nearly 45 years after it was introduced (Wilhelm *et al.*, 2005). Offspring (G3 = Grandchildren of G1, children of G2) were asked to complete the PBI on the specific parent (how the offspring experienced being parented by her/his parents). The PBI consists of 25 four-point items assessing the perception of parenting style/behaviors of each parent. Participants indicated how much their parents were like each statement on a 4-point scale (0 = Not at all to 3 = Always). The respondents answer the questions based on how they remember their parents during their first 16 years of life. Parents were evaluated along two dimensions, Care (sensitive and responsive parenting) and Overprotection (intrusive and excessive controlling parenting), with separate norms on each dimension for mothers and fathers. Parental Care subscale was used in the current study since research has shown that the parental Care dimension found to be more predictive for offspring depressive symptoms and diagnosis (moderate to large effect size) than the 'Overprotection' dimension (Alloy *et al.*, 2006). Still, after completing running the analyses based on our hypotheses, we examined the interactive effect of parental 'Overprotection' and parent's strength of CBG WM connections on concordance, and consistent with the literature, there were no significant effect of overprotection. Although the responses rely on the subjects' own recollections, the validity of the instrument has been supported by studies that show that subjects' ratings correlate strongly with ratings of their parents themselves, siblings and impartial raters, including observational assessments of parental behavior (Parker, 1983; Steiger *et al.*, 1989). Age, sex and social class have minimal effect on scores. Also, by administering the PBI to depressed patients and repeating this when they remitted, it has been shown that the Care and Overprotection scores were stable over 20 years (Wilhelm *et al.*, 2005; Murphy *et al.*, 2010). In addition, to make sure the effect of PBI was not confounded by offspring age and sex in our sample, we used age and sex of the participants when they rated their relationships with their parents as covariates, and also we did not find any significant association between age and sex and rating of parental Care ($r = 0.138$, $P = 0.371$; $t_{(1,42)} = -0.126$, $P = 0.9$, respectively).

Analytic strategy

Parent–offspring concordance was defined as the standardized beta coefficient corresponding to the effect of parental WM connectivity on offspring WM connectivity (the number of fiber tracts at the level of streamlines) obtained from a generalized linear model. We used the generalized estimating equation (GEE) statistical approach (Liang and Zeger, 1986) in the framework of a generalized linear model to adjust for potential correlation of outcomes between siblings in the same family. These potential correlations among the outcomes were modeled as exchangeable. We controlled for familial (G1 depression status) risk status (High *vs* Low), offspring MDD status and parents' and offspring's age and sex (including parental MDD in Hypothesis 1). Because 48 connections (6 cortical regions × 4 basal ganglia regions × 2 hemispheres) were tested per hypothesis (Hypotheses 1–3), and 3 connections for Hypothesis 4, our four hypotheses yielded a total of 147 tests. In situations such as this, it is appropriate to control the false discovery rate (FDR) using the Benjamini-Hochberg (B-H) procedure (Benjamini and Hochberg, 1995), which is also the most common procedure in MRI studies. Under this procedure, the adjusted alpha level that yields an overall FDR of 5% is 0.01, so we report all *P*-values less

than 0.01 as significant, under this adjustment. We used the PROC GENMOD procedure in SAS 9.4 (SAS Institute, NC, USA) to conduct these analyses.

Results

Intergenerational concordance in WM connectivity

We first sought to examine associations (concordance) in WM connectivity in CBG circuits between parents and their offspring (Hypothesis 1). We z-scored parameter estimates and conducted a series of GEE analyses and used familial (G1 depression status) risk status, parent and offspring MDD status, sex and age as covariates. Results of the significant associations are shown in Table 2 (for all tested associations, see Table S2), revealing several positive associations between parent's and offspring's strength of WM connections within the CBG circuits; between the NAcc and FG, ITG and TP, between the caudate and FG and STS, between the pallidum and TPJ/supramarginal gyrus (SMG) and TP, and between putamen and FG and TPJ, $P < 0.05$ FDR-corrected for multiple comparisons.

Parental lifetime-MDD and parental Care as moderators

To test the moderating effects of parental history of depression (Hypothesis 2) and parental Care (Hypothesis 3) variables on parent–offspring concordance, we ran GEE analysis for each of the CBG connections. In each model, we entered parent lifetime-MDD status and parental Care as moderators of the effect of parental WM connectivity on offspring WM connectivity, and used familial (G1) risk status, offspring's MDD status, parent and offspring sex and age as covariates. Significant findings ($P < 0.05$ FDR corrected for multiple comparisons) are presented in Table 2 (for all tested interactions, see Table S2). As can be seen, parent MDD interaction terms were significant in six CBG connections—L NAcc-MTG, L Putamen-FG, R putamen-TPJ, R pallidum-MTG, R pallidum-STS, and R pallidum-TPJ, indicating that dyads with a depressed parent and dyads without a depressed parent differed in the concordance between parent and offspring CBG connectivity. To illuminate the nature of the interactions, we plotted regression slopes of parent's WM connectivity on the offspring's WM connectivity for dyads with and without a lifetime-MDD parent (Figure 2). Simple slope analyses revealed that while among dyads with a never-depressed parent there were significant positive associations between parent's and offspring' strength of WM connections, there were no such associations among dyads with a depressed parent. As for parental Care, interaction terms were significant in 12 CBG connections; R NAcc-STS, L caudate-fusiform, L caudate-TP, L caudate-TPJ, L putamen-ITG, L putamen-TPJ, R pallidum-fusiform, R pallidum-MTG, R pallidum-TP, R pallidum-STS, and L/R pallidum-TPJ, indicating that the better the quality of early caregiving (e.g. more sensitive and responsive parenting) the greater the dyadic concordance in parent and offspring WM connectivity.

Parental lifetime-MDD × early parental Care interaction

Finally, to test Hypothesis 4 whether high levels of early parental Care can protect the dyadic concordance from the effects of parental lifetime-MDD, we ran GEE analyses for the right Pallidum-MTG, right Pallidum-STS and right Pallidum-TPJ/SMG connections, the three CBG connections moderated by both parental lifetime-MDD and parental Care. To estimate the degree

of concordance (similarity), we subtracted parents' WM connectivity from the offspring's WM connectivity and divided the absolute differences by the absolute sum of the two values (Törnqvist *et al.*, 1985). In each model, we entered parent lifetime-MDD status, parental Care and their interaction as predictors of the parent–offspring degree of concordance, and used familial (G1) risk status, offspring's MDD status, parent's and offspring's age and sex as covariates. Significant parent lifetime-MDD × parental Care interactions were found predicting concordance in the right pallidum-STS connectivity (ß = − 0.45, SE = 0.19, $P = 0.01$) and in the right pallidum-MTG connectivity (ß = − 0.74, SE = 0.12, $P < 0.0001$). No significant interaction was found predicting concordance in the right Pallidum-TPJ/SMG connection (ß = − 0.34, SE = 0.25, $P = 0.1$). To illuminate the nature of significant interactions, we created bar charts of parental Care (high *vs* low) on parent–offspring concordance for dyads with a depressed parent and without a depressed parent and ran GEE regressions to examine associations between variables. As shown in Figure 3A, degree of right Pallidum-STS WM concordance was correlated with parental lifetime-MDD under low parental Care, (ß = 0.35, SE = 0.14, $P < 0.01$), indicating greater neural concordance among dyads with a non-depressed parent compared with dyads with a depressed parent, but no association was found under high parental Care (ß = 0.09, SE = 0.18, $P > 0.05$). No difference was found among dyads with and without a depressed parent in the degree WM concordance between low and high parental Care (ß = 0.31, SE = 0.25, $P > 0.05$; ß = − 0.002, SE = 0.10, $P > 0.05$, respectively). Dyads with a depressed parent and low parental Care had the weakest neural concordance. As shown in Figure 3B, degree of right Pallidum-MTG WM concordance was correlated with parental lifetime-MDD under low parental Care (ß = 0.48, SE = 0.14, $P < 0.01$), while no association was found under high parental Care (ß = 0.33, SE = 0.49, $P > 0.05$). Also, only among dyads with a depressed parent, there was a significant difference in the degree of WM concordance between low and high parental Care (ß = 0.49, SE = 0.18, $P < 0.001$), with a weaker concordance under low parental Care compared with high Care. No difference was found among dyads with a non-depressed parent (ß = − 0.13, SE = 0.41, $P > 0.05$). Again, dyads with a depressed parent and low parental Care had the weakest neural concordance.

Finally, in order to determine whether the current findings of the disruption in concordance among dyads with a depressed parent may be a risk factor for the intergenerational transmission of psychopathology and social impairment, or a consequence of parent and offspring depression, we conducted a second set of analyses, excluding all dyads with depressed offspring, and comparing two groups of dyads: non-depressed dyads (never-depressed parents and their never-depressed offspring) and at-risk dyads (depressed parents and their never-depressed offspring). Our findings were mainly consistent for all four hypotheses, suggesting disruption in concordance may be a potential mechanism underlying the intergenerational risk of depression. Details concerning the results of these analyses are presented in online supplementary material (see Supplementary Table S4,5).

Discussion

One of the central pillars of human social development is the ability to be attuned to the social cues of others, including sharing others' emotions and the ability to take into account

Table 2. White matter connections in CBG circuits showing significant associations* (concordance) between parents (with and without lifetime-MDD) and their offspring (with and without lifetime-MDD) and significant interaction effects* (a) between parent's lifetime-MDD status × parent WM connectivity and (b) between parental Care × parent WM connectivity in predicting offspring WM connectivity

Basal ganglia region	CBG WM connections		L hemisphere			R hemisphere	
			Standardized ß (SE)	Z	P-value	Standardized ß (SE)	Z	P-value
NAcc—	Fusiform gyrus	Parent WM connectivity	0.38 (0.08)	4.35	<0.0001	-	-	-
		(a) Parental MDD × Parent WM connectivity	-	-	-	-	-	-
		(b) Parental Care × Parent WM connectivity	-	-	-	-	-	-
	ITG	Parent WM connectivity	0.34 (0.13)	2.59	0.001	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
	MTG	Parent WM connectivity	0.42 (0.12)	3.26	0.001	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
	Temporal pole	Parent WM connectivity	-	-	-	0.48 (0.12)	3.9	<0.0001
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
	STS	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
	TPJ/SMG	Parent WM connectivity	-	-	-	1.57 (0.53)	2.9	0.003
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
Caudate	Fusiform gyrus	Parent WM connectivity	0.39 (0.14)	2.75	0.001	-	-	-
		a	-	-	-	-	-	-
		b	0.45 (0.16)	2.83	0.004	-	-	-
	ITG	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
	MTG	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
	Temporal pole	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	-	-	-
		b	1.03 (0.32)	3.17	0.001	-	-	-
	STS	Parent WM connectivity	0.24 (0.11)	2.59	0.01	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-

Table 2. (Continued)

Basal ganglia region	CBG WM connections		L hemisphere			R hemisphere		
Putamen	TPJ/SMG	Parent WM connectivity	-	-	-	-	-	-
		a	0.86 (0.44)	1.93	0.005	-	-	-
		b	-	-	-	0.28 (0.09)	3.02	0.002
	Fusiform gyrus	Parent WM connectivity	-	-	-	-	-	-
		a	0.42 (0.12)	3.48	0.0005	-	-	-
		b	-	-	-	-	-	-
	ITG	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
	MTG	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	-	-	-
		b	0.33 (0.08)	3.87	0.0001	-	-	-
	Temporal pole	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
	STS	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
	TPJ/SMG	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	0.57 (0.09)	6.16	<0.0001
		b	0.41 (0.08)	4.93	<0.0001	0.25 (0.08)	3.01	0.002
Pallidum	Fusiform gyrus	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	1.42 (0.50)	2.83	0.004
	ITG	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	-	-	-
		b	-	-	-	-	-	-
	MTG	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	0.30 (0.13)	2.23	0.002
		b	-	-	-	0.52 (0.23)	2.26	0.002
	Temporal pole	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	0.30 (0.07)	4.18	0.0002
		b	-	-	-	0.38 (0.11)	3.34	0.0008
	STS	Parent WM connectivity	-	-	-	-	-	-
		a	-	-	-	0.33 (0.13)	2.55	0.001
		b	-	-	-	0.58 (0.17)	3.30	0.001
	TPJ/SMG	Parent WM connectivity	0.49 (0.13)	3.65	0.002	0.24 (0.09)	2.56	0.01
		a	-	-	-	0.56 (0.26)	2.12	0.003
		b	0.52 (0.09)	5.29	<0.0001	0.85 (0.27)	3.13	0.001

ªSignificant associations and interactions after $P < 0.05$ FDR correction ($P \leq 0.01$); '-' indicates a non-significant association and interactions after FDR correction. For full table with all tested association and interactions, see Supplementary Information, Table S2.
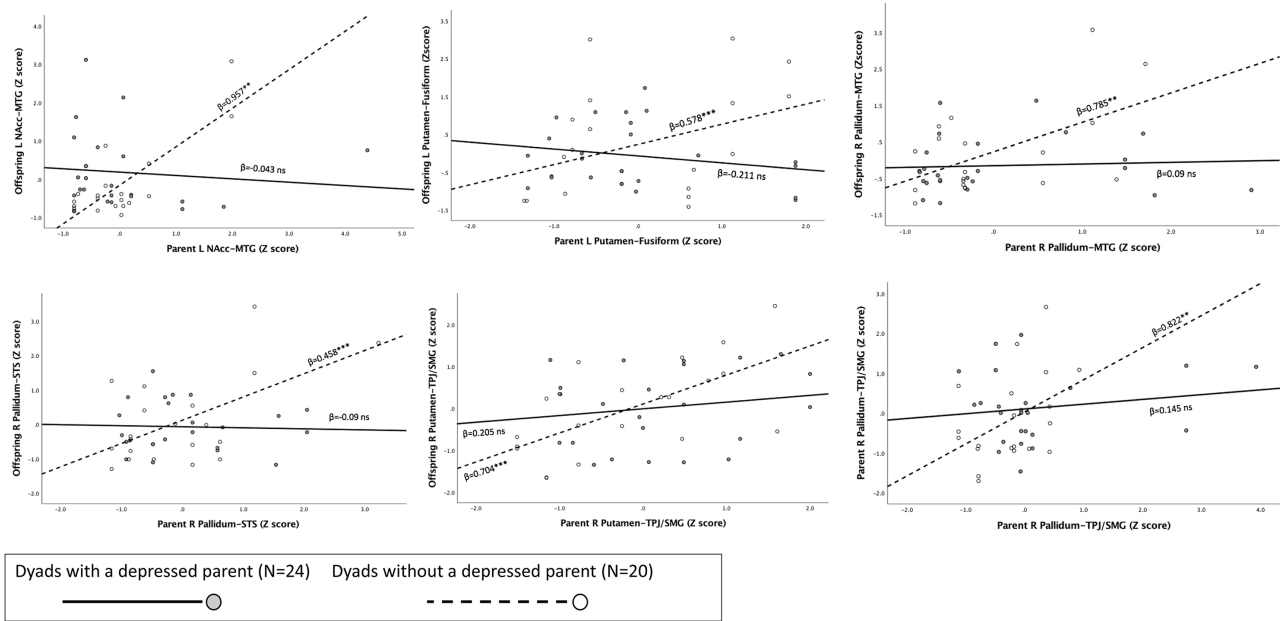
Fig. 2. Graphical depiction of association between parent and offspring CBG WM connectivity by parent's lifetime-MDD status, with stronger associations evident in dyads with a never-depressed parent. **P < 0.01; ***P < 0.001, ns, non-significance.
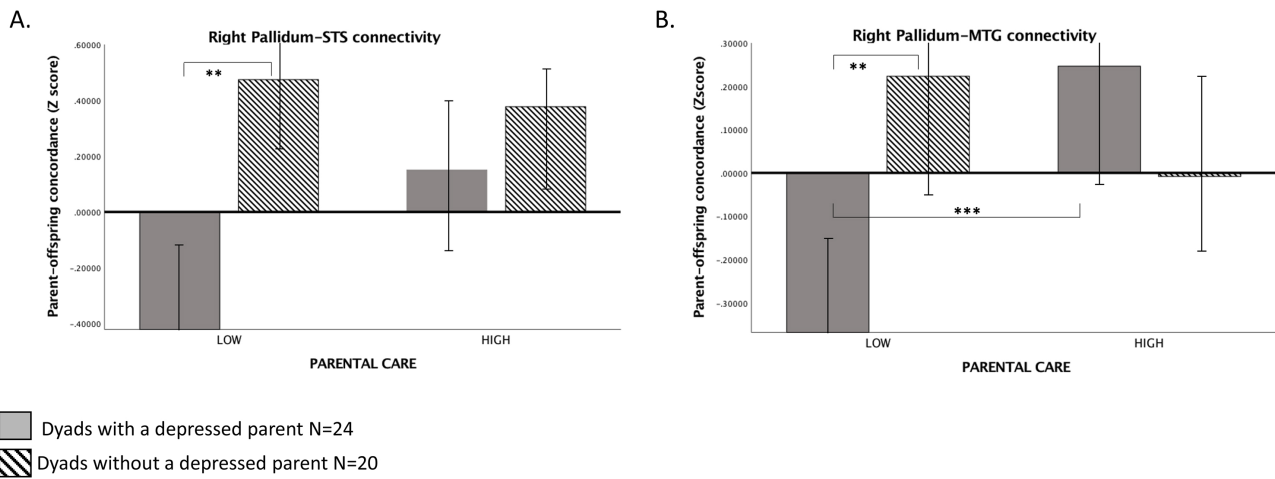

Fig. 3. Graphical depiction of parental lifetime-MDD by parental Care interaction predicting dyadic concordance in parent and offspring WM pallidum-MTG and pallidum-STS connectivity. **P < 0.01; ***P < 0.001. N dyads (Low Care/Dyads with a depressed parent) = 13; N dyads (Low Care/Dyads without a depressed parent) = 11; N dyads (High Care/Dyads with a depressed parent) = 11; N dyads (High Care/Dyads without a depressed parent) = 9.

others' perspectives and thoughts, which is first experienced and formed in the context of early parent-child relationship and represented at physiological levels (Gordon *et al.*, 2020a, b; Decety, 2015). Such affective, behavioral and physiological attunements protect individuals from stressful experiences, unpredictable environment and from developing psychopathology from infancy to elderly (Barton et al., 2013; Stern et al., 1985; Tops et al., 2014; Feldman, 2020).

To our knowledge this is the first study to examine dyadic concordance in CBG circuits in a sample of mothers and fathers with and without a lifetime history of MDD and their offspring, and the first to show how neural concordance varies by risk factors—parental depression and poor early caregiving. We also examined if higher levels of parental Care, as perceived by the

offspring during the first 16 years of life, provide a protective buffer against the attenuated concordance in WM connections associated with parental depression. Our study provides the first neurobiological evidence that parent–offspring concordance in specific WM connections between basal ganglia and temporal cortical areas implicated in mentalizing functions and which support social attachments (Meaney, 2001) is disrupted among families with a parental history of MDD, and its degree is associated with quality of early parental caregiving.

The basal ganglia structures are implicated in human attachments, and play a central role in the formation and maintenance of mother-offspring bonding, father-offspring bonding, co-parenting, romantic love and close friendship, due to the integration of OT and DA in these structures which ignites

relationships, and imbuing attachments with motivation and rewarding (For review see: Feldman, 2015; Swain and Ho, 2017). However, the basal ganglia structures do not only maintain close interconnectivity, but are also connected via multiple ascending and descending projections to cortical regions, including the temporal cortex (Fareri and Delgado, 2013; Swain and Ho, 2017). Such connectivity allows the integration of later-evolving cortical structures implicated in higher order socio-affective processes with the conserved, automatic brain circuitry underpinning mammalian maternal care, motivation and novelty and reward seeking (Tops *et al.*, 2014; Feldman, 2015). It has been suggested that CBG circuits support human ability to appreciate social familiarity over novelty seeking, which is a vital process in promoting resilience and sociality and protecting against stress and psychopathology (Rilling and Young, 2014). For instance, in a recent fMRI longitudinal study, Abraham and colleagues (2016, 2017) found that connectivity between limbic network, including the basal ganglia structures, and cortical structures implicated in social cognition, when parents watched videos of their infants, shaped children's OT response in preschool years, which in turn supported maturation of the child's social competencies at school-entry. Also, parental CBG connectivity during infancy predicted lower child externalizing symptoms at 6 years as mediated by collaborative co-parenting in preschool years. Finally, Atzil and colleagues (2011) found that sensitive mothering was underpinned by greater connectivity between limbic structures and frontal and temporal regions.

In search for specific CBG pathways that define the integration of subcortical nuclei with cortical structures, our findings highlight three important aspects of human dyadic concordance and its links with psychopathology and social bonding. First, while using parental and offspring MDD status as covariates, we found concordance in associations between parent and offspring integrity of WM tracts that connect the basal ganglia nuclei with temporal regions (FG, ITG, TPJ, STS and TP). Second, we found that parental lifetime-MDD status and parental Care moderated these parent–offspring associations. Specifically, among dyads with a never-depressed parent, parents' integrity of WM tracts that connect the basal ganglia nuclei with the temporal regions (STS, FG, MTG, TPJ and TP) were positively associated with those of their offspring. In contrast, among dyads with a depressed parent, no such associations were found. Also, higher levels of parental Care were associated with greater positive associations between parent and offspring integrity of WM tracks that connect the basal ganglia nuclei with FG, STS, MTG, ITG, TPJ and TP. Finally, parental Care was found to moderate the associations between parental lifetime-MDD and the degree of dyadic concordance in right pallidum-MTG and pallidum-STS. Under low levels of parental Care, greater concordance was found for dyads with a non-depressed parent compared with dyads with a depressed parent, while no differences between the two groups were found under high levels of parental Care. The weakest concordance was found among dyads with a depressed parent who also provided low parental Care, indicating that early parental caregiving may protect the dyadic concordance from the effects of parental lifetime-MDD. Also, for the right pallidum-MTG connection, among dyads with a depressed parent there was a significant difference in the degree of WM concordance between low and high parental Care, with a weaker concordance under low parental Care compared with high Care. No difference was found among dyads with a non-depressed parent.

Human attachment bonds have evolved on the basis of the early parent–offspring bonding (Hrdy, 2009), and are not merely bodily relations, but also brain-relations, 'neural relations'. Human social bonding and affiliation throughout life are highly dependent on affect sharing, biobehavioral synchrony, self-other awareness, mental flexibility, perspective-taking, memory and language (Abraham *et al.*, 2014; Decety, 2015; de Waal and Preston, 2017; Feldman, 2017). Our finding of dyadic concordance in parent–offspring CBG WM connections and its link with early-life parent–offspring relationship adds to previous animal and human studies documenting the unique fit between biological and social processes that forms the specific attachment bond between parents and offspring (Ebisch *et al.*, 2012; Creaven *et al.*, 2014; Feldman *et al.*, 2010, 2011). In line with our results, recent neuroimaging studies reported stronger brain-to-brain coupling in basal ganglia and temporal cortex as reciprocity, familiarity and cooperation increased (Baker *et al.*, 2016; Reindl *et al.*, 2018), associations between neural coupling and affectionate bond (Atzil *et al.*, 2012; Levy *et al.*, 2017) and pain reduction (Goldstein *et al.*, 2018). For instance, a recent MEG study found that only during episodes of behavioral synchrony, compared with nonsynchrony, mother's and child's STS gamma power was coupled (Levy *et al.*, 2017), two hyper-scanning fNIRS studies showed neural concordance in TPJ only during social gaze interaction, which was also related to the degree of dyadic reciprocity and cooperation (Mu *et al.*, 2016; Tang et al., 2016), and a hyper-scanning EEG study found a neural concordance among partners, but not strangers, localized in temporal-parietal structures, which was linked to behavioral synchrony among couples (Kinreich *et al.*, 2017). It has previously been shown that structural organizations follow the magnitude of neural activity, which means that tracts that are used more (function) will become denser and more organized (structure) and both are associated with behavioral performance (Bennett and Rypma, 2013; Burzynska *et al.*, 2013). Therefore, if structures are concordant, it stands to reason that there are also functional parallels, as found in previous studies examining coupling of neural activity. It will be necessary to test this assumption by demonstrating, for example, that concordant DTI measures correlate with a behavior measured in both the parent and the child.

We also found that parental depression disrupted parent–offspring WM concordance in CBG connections. This finding is in line with evidence showing that parental depression is associated with attenuated behavioral parent-child concordance (Field *et al.*, 1990; Murray and Cooper, 1996; Tronick and Reck, 2009; Granat *et al.*, 2017), which extends to the levels of hormonal (Merwin *et al.*, 2017), and autonomic (Woody *et al.*, 2016) functioning. It is worth noting that the connections between the basal ganglia and the temporal lobe, including the TPJ, TP and STS, are human-specific and stronger among humans compared with non-human primates, including chimpanzees, probably due to their role in social-interactive processes such as language, action observation and ToM (Innocenti *et al.*, 2016; de Waal and Preston, 2017). Indeed, parents suffering from depression tend to speak less, make less eye contact, generally slower in their responses to their children and exhibit lower positive affect and limited empathic understanding (Hummel *et al.*, 2016; Granat *et al.*, 2017).

Of significant interest is our finding that higher levels of early parental Care as, as reported by the offspring, buffered the attenuated neural concordance in the right pallidum-MTG and pallidum-STS associated with parental depression. This finding confirms the central role of the basal ganglia and the STS and MTG in the processing of attachment and social stimuli as well as their sensitivity to early environmental experiences (Brunet *et al.*, 2000; Cecchini *et al.*, 2013; Shields *et al.*, 2019). Also, finding

is consistent with previous animal and human studies showing that social attachments, including parent–offspring bonding, pair-bonding and friendship, buffer against psychopathology and the consequences of stressful events, including exposure to parental depression (Flykt *et al.*, 2010; Pratt et al.,2015; Schury *et al.*, 2017; Vakrat *et al.*, 2018).

The pallidum comprises a rich neural circuitry of diverse cell types that shape both motor and non-motor features of behavior (Obeso *et al.*, 2008). In recent years, a plethora of studies has demonstrated that the pallidum is far more than a simple motor-control nucleus (Gittis *et al.*, 2014). Since the pallidum is rich in OT and DA receptors (Lim *et al.*, 2004; Avila *et al.*, 2020), it processes reward and motivational-related signals in general (Hong and Hikosaka, 2008), and specifically those related to social attachment (Bartels and Zeki, 2004; Leibenluft *et al.*, 2004). The pallidum supports maternal and paternal caregiving (Rilling and Mascaro, 2017), as well as children's secure attachment to their parents (Choi *et al.*, 2018). The STS is a central region of the social cognition network, playing a vital role in mentalizing, parental care, biological motion, social goal interpretation, prediction making, and updating regarding others' behavior (Gordon *et al.*, 2013; Abraham *et al.*, 2014; Wang *et al.*, 2018). The MTG, bounded by the STS above, is part of the 'language network', and together with the STS and subcortical structures, including the basal ganglia (Tomasi and Volkow, 2012) supports goal-directed action targeted at another person, and shows tight relationship with ToM functioning (Kandylaki *et al.*, 2015), with familiarity in the context of social attachment (Gobbini *et al.*, 2004) and with affective communication conveyed by empathic decoding of others' pain experience (Lang *et al.*, 2011). Connectivity between the basal ganglia and MTG and STG have been shown to be associated with language processing (Booth *et al.*, 2007) and with attention to faces of social partners (Powell *et al.*, 2018)—two central components of human socio-affective communication and bonding (Hari and Kujala, 2009). Still, future studies should focus on the connections between the pallidum and the STS/MTG to obtain a better understanding of the functional and structural connectivity between these regions in social contexts in general, and in the context of early-life rearing experiences, in particular.

Finally, by excluding all dyads with depressed offspring and examining parent–offspring concordance between depressed and never-depressed parents and their never-depressed offspring in supplementary analyses, we suggest that such disruption in neural concordance within the CBG circuits may be a potential mechanism underlying the intergenerational risk of depression.

While this is the first study to examine dyadic concordance in CBG connections in a sample of parents with and without a history of MDD and their offspring, and the first to show how dyadic concordance in WM connectivity varies by parental risk factors using unique dyadic datasets with richly characterized clinical and environmental data over-time, several study limitations merit consideration. First, since our findings are based on a relatively small sample of parent–offspring dyads, future studies with a larger sample size are needed to further elucidate the nature of parental depression on neural concordance between parents and their offspring. Second, our findings are correlational in nature and do not suggest causality, and we are unable to test the directionality of our findings. Third, the sample was of European ancestry, as was the norm for family studies when the project originated; generalizability of the findings across racial and ethnic groups should not be assumed. Fourth, while the validity of the PBI has been supported by studies showing that subjects' ratings correlate strongly with ratings of their parents

themselves, siblings and impartial raters (Parker, 1984; Parker *et al.*, 1979; Steiger *et al.*, 1989), parental Care was based merely on offspring's perception of relationship with their parents. Therefore, the interpretation of the results could be influenced by the fact that the instrument was self-reported and reflect a bias in the perception of parenting style. This could be particularly evident for our sample, in which the range of age of participants was broad. Future studies may consider integrating self-report and observational measures (e.g. coding parent–offspring social interaction) to evaluate parent–offspring bonding during early childhood.

To summarize, the present study provides important contributions to the extant literature by documenting parent–offspring concordance in WM structural connectivity across different developmental stages, which was found to be sensitive to parental psychopathology and early parental caregiving and provide another step in pinpointing the neurocircuitry that supports coordination between parent and offspring. Recent models in social neuroscience have proposed moving beyond studying neural processes at the within-individual level to considering coordinated neural activity across multiple individuals and how such neural coupling underpin the ability to form and maintain social bonds across the lifetime (Hari, 2017). Hopefully, our findings may stimulate more experimentally controlled studies to further examine dyadic concordance in other neurocircuitries, such as those implicated in fear, anxiety and aversive social processing. Future studies should explore how brain connectedness links with other psychiatric disorders, how other environmental experiences and disruptions of other social bonds interrupt brain coupling and should investigate other conditions under which brain synchronization operates to hinder or facilitate social bonding and functioning. Our findings may have important implications for advancing our understanding of disorders characterized by neural and behavioral disturbances in social cognition, such as major depression, as well as clinical implications for the development of early relationship-focused interventions for depressed parents and their children to reduce the risk for psychopathology among at-risk populations.

Supplementary data

Supplementary data are available at SCAN online.

Disclosures

Author contributions

Substantial contributions to the conception or design of the work or the acquisition, analysis or interpretation of data for the work (E.A., M.M.W., P.J.W., J.C., J.P. and A.T.); and Drafting the work or revising it critically for important intellectual content (E.A., M.M.W., P.J.W., J.P. and A.T.); and Final approval of the version to be published (E.A., M.M.W., P.J.W., M.T.V., J.P. and A.T.);

and Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (E.A., M.M.W., P.J.W., J.C., M.T.V., J.P. and A.T.).

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