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PATTERNS OF ANTERIOR VESUS POSTERIOR WHITE MATTER FRACTIONAL ANISOTROPY CONCORDANCE IN ADULT NONHUMAN PRIMATES: EFFECTS OF EARLY LIFE STRESS

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Abstract

Introduction—Functional neuroimaging studies report global prefrontal dysconnectivity in mood disorders, supporting the notion of widespread disruptions in brain networks. Microscopic alterations in white matter (WM) tracts -- which possess neuroplastic properties and play a central role in brain connectivity -- are interrogated herein in the context of brain dysconnectivity. Early life stress (ELS), an antecedent to human mood disorders, induces WM alterations in volumetrics

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COI:

Dr. Mathew has been named as an inventor on a pending use-patent of ketamine for the treatment of depression. Dr. Mathew has relinquished his claim to any royalties and will not benefit financially if ketamine were approved for this use.

There are no COIs for JDC, VK, CGA, TDP, GP, DC and CT

Disclosures

Dr Coplan is a speaker for Pfizer, Forest, BMS, GSK, Eli Lilly and Sunovion. He has received grants from Pfizer Pharmaceuticals, GSK, Corcept and Neurocrine. He has served on the advisory board of Pfizer, Otsuka, Lundbeck and Corcept.

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and integrity. We hypothesized that nonhuman primate infants exposed to ELS would exhibit persistent impairments in both frontal and posterior concordance of WM integrity, therefore contributing to global brain dysconnectivity.

Methods—Using a 3T-MRI, diffusion tensor imaging (DTI) was performed on 21 adult male Bonnet macaques, 12 of whom had been raised under variable foraging demand (VFD) conditions and nine of whom had been raised under normative conditions (Non-VFD). As representative of anterior regions, fractional anisotropy (FA) concordance between anterior corpus callosum (ACorpusC) and anterior limb of the internal capsule (ALIC) was examined. For posterior regions, FA concordance between posterior corpus callosum (PCorpusC) and posterior limb of the internal capsule (PLIC) and between PCorpusC and occipital WM was examined. Examination of posterior FA was explored in the context of frontal markers of neuroplasticity.

Results—A concordant relationship for FA between left ALIC and ACorpusC was evident in Non-VFD-reared subjects, but significantly absent in VFD-reared subjects. For left posterior regions, FA concordance between PLIC and PCorpusC and occipital WM and PCorpusC was evident in VFD-reared and not Non-VFD-reared subjects. The posterior concordance in VFD was significantly distinguishable from the deficit in anterior concordance FA in VFD.

Conclusions—The findings support the view that disrupted emotional integrity of the maternal-infant attachment process affects normative synchronous development of frontal white matter tracts but creates errant posterior concordance and also disrupts an inverse relationship between posterior white matter tracts and markers of neuroplasticity. We provide preliminary evidence that a concordant relationship between capsular-callosal FA may become discordant, providing a putative mechanism for prefrontal functional brain dysconnectivity.

BACKGROUND

Childhood abuse and neglect is a major antecedent for a variety of human adult disorders including mood (1–4) and anxiety disorders (2, 5), metabolic syndrome (6), chronic pain disorders (4, 7, 8) and cardiovascular disease (3, 9, 10). Preclinical models of early life stress (ELS) have mostly utilized rodents (11) and nonhuman primates (12, 13) primarily manipulating the integrity of maternal care (14). We have utilized an animal model of ELS in bonnet macaques exposed to maternal variable foraging demand (VFD), a paradigm in which infants are reared by mothers subjected to an experimentally-induced perception of food uncertainty without caloric deprivation (15). VFD-reared subjects exhibit timidity (16) and loss of “behavioral plasticity” -- a term applied to adaptive modifications of behavior (17) -- in response to a human intruder in comparison to healthy controls (18). Moreover, VFD-reared macaques exhibit persistent elevations in CSF concentrations of the stress neuropeptide, corticotropin releasing-factor (CRF) (19), and a myriad of other neurotransmitter (20), metabolic (21), neuroanatomical, including corpus callosum cross-sectional area deficits (16, 22), molecular (23, 24) and neuroplastic alterations (21). This extensive array of alterations each appear capable of contributing to the affective distress observed in VFD-reared subjects (15) and replicate abnormalities observed in human anxiety and mood disorders (25). However, whether these discrete alterations in VFD-reared subjects interact as an aberrant neural circuitry has not been previously addressed.

More recently, psychiatric disorders in general, and mood disorders in particular, have been hypothesized to stem from disrupted neural computations across networks of regions (26). Recent functional neuroimaging studies have reported global prefrontal dysconnectivity in bipolar I disorder (27), major depressive disorder (MDD) (28), obsessive compulsive disorder (OCD) (29) and schizophrenia (30), supporting the notion of widespread disruptions in brain networks in severe psychiatric disorders (27). Abnormal neuroplasticity and cellular resilience (31) have been invoked to produce impairments in these distributed neural networks (32). A study in major depressive disorder indicated that methylation of the BDNF promoter region was associated with reduced regional white matter integrity (33), suggesting that white matter may also be vulnerable to neurotrophic compromise. One hypothesis – based on studies in patients with generalized anxiety disorder – is that posterior regions, such as the occipital lobe, may be relatively hyperactive or hypertrophied whereas anterolateral regions, such as the hippocampus and prefrontal cortex, are hypoactive and hypotrophic (34). Treatment studies using riluzole – an antiglutamatergic agent – show anteroposterior divergent structural and molecular effects in GAD and bipolar depression patients (34–37). Anteriorly, treatment response is associated with a parallel increase in gray matter volume and concentrations of N-acetyl-aspartate (NAA), a marker of neuronal integrity (35). Posteriorly, anxiolytic effects were associated with reduced occipital gray matter volume and NAA (34–36). Moreover, a reduction in occipital, but increase in prefrontal, glutamate levels following treatment of patients with MDD correlated with successful anxiolytic and antidepressant response (38, 39). The implications of this anterior/posterior divergence in psychiatric disorders and its treatment response, interfaced with the notion of global brain dysconnectivity remains to be elucidated.

Fractional anisotropy (FA), a measure derived from diffusion tensor imaging (DTI) (40), assesses the degree of directionality of water diffusion within the white matter tracts (41). FA is relatively high in parallel tracts of axons, whereas FA is relatively reduced in demyelinating conditions. (42) Reduced FA in the absence of gross pathology of white matter may represent a subtle form of impairment of normative structural organization of axons (43) and potentially contribute to global brain dysconnectivity. Reversal of reduced frontal WM FA in late-life depression through antidepressant intervention--electroconvulsive therapy —implies that WM tracts possess recuperative neuroplastic properties (44). Preclinical studies indicate that BDNF enhances WM integrity by increasing concentrations of myelin basic protein and facilitating oligodendrocyte proliferation (45, 46). Anticevic et al (in press) have articulated that “decreased global brain connectivity in a disease state might suggest decreased participation of a particular brain region in broader networks, whereas increased global brain connectivity might suggest a pathological broadening or synchronization of functional networks.”

With respect to white matter, concordance of FA between distinct, anatomically unrelated regions invokes the presence of a common neuroplastic influence with putatively salutary functional consequences. In the current study, as representative of anterior regions, FA concordance between anterior corpus callosum (16, 47) and anterior limb of the internal capsule (23) was examined. The anterior limb of the internal capsule contains fibers running from the thalamus to the frontal lobe and fibers connecting the cortex with the corpus striatum (23). From the anterior corpus callosum, fibers radiate from the genu to the

prefrontal cortex (48). In the case of psychopathology, a concordant relationship between capsular-callosal FA may become discordant, providing a mechanism, at least in part, for prefrontal brain dysconnectivity. We hypothesized that between-region concordance of FA could conceivably reflect neuroplastic homogeneity, facilitating orderly distribution of brain networks, whereas neuroplastic inhomogeneity would facilitate dysconnectivity and negative affective states. We have already shown that mean FA of the anterior limbs of the internal capsule correlates inversely with right and left amygdala volume, a marker of early life stress, specifically in VFD versus Non-VFD (22). In addition, elevations of CSF 5-HIAA, a putative indicator of reduced serotonin neurotransmission, inversely predicted mean FA of the anterior limbs of the internal capsule but only in VFD-reared versus normally-reared subjects (20).

As representative of posterior regions, FA concordance between posterior corpus callosum (16, 47) and posterior limb of the internal capsule (49) and between posterior corpus callosum and occipital white matter (23) was examined. The posterior body of the corpus, known as the splenium (50), communicates somatosensory information between the two halves of the parietal lobe and the visual cortex at the occipital lobe. The posterior limbs of the internal capsule carry the corticospinal tracts (49) whereas the occipital white matter projects to the visual cortex (51). We hypothesized that FA concordance in posterior regions would be relatively more evident in VFD-reared versus control subjects, confirming an anterior/posterior divergence. As an auxiliary hypothesis, we postulated that FA of posterior ROIs would correlate positively with indicators of reduced neurotrophic status and inversely with stress markers. We would therefore provide additional evidence of an anterior/posterior WM FA divergence as relates to non-WM structures.

METHODS

Subjects

21 adult male Bonnet Macaques (*Macaca Radiata*) served as subjects. Using a 3-T MRI, DTI scans were obtained on 22 subjects but data from one scan was lost due to technical difficulties. Subjects were approximately five years old at the time of the scan (see Table 1) corresponding to young adulthood in this species. Of the 21 subjects on whom DTI data was available, 12 had been raised under VFD conditions whereas nine subjects were raised under normative conditions. Data were acquired for age, weight, total brain volume and white matter volume (see table 1). There were no mean differences between groups for age, weight and total brain volume (all $p > 0.1$). The primary analysis of the DTI data has been published (23) and the current report comprises a secondary analysis. Data on neurogenesis rates (52), hippocampal volume (16) and amygdala volume (22) have been reported on previously in the identical cohort.

Subjects were individually-housed in the SUNY-Downstate Nonhuman Primate Facility. The study was approved by the Institutional Animal Care and Use Committees of SUNY-Downstate and Mount Sinai School of Medicine (MSSM).

VFD procedures (19)

Mother-infant dyads were group-housed in pens of 5–7 dyads each and stabilized for at least four weeks prior to VFD onset. After infants reached at least 2-months of age, dyads were subjected to a standard VFD procedure that involved 8 alternating 2-week blocks in which maternal food availability was either readily obtained (low foraging demand (LFD) or easy phase) or more difficult (high foraging demand (HFD) phase).. Supporting the view that the VFD effects are mediated by unpredictable, rather than difficulty of maternal foraging conditions, we have previously shown that a persistently difficult high foraging demand did not, in contrast to the unpredictable VFD condition, produce sustained increases in CSF CRF concentrations.(13) Disruption of normative patterns of maternal-infant attachment are cited to underlie the sustained effects on VFD offspring.(19) Difficulty in obtaining food for the mothers was achieved through the use of a foraging cart, a device in which food rations can be hidden in wood chip, with apertures on the sides of the cart for foraging. No caloric restriction is present in the VFD procedure, and normal maternal and infant weights are maintained.(53) Following the VFD procedures, offspring were first housed with their mothers and then in standard peer social groups once they had reached the juvenile phase of development. Following the infant phase of development, there were no significant experimental manipulations of either the VFD or NON-VFD offspring that could confound the VFD-rearing effects.

Transport, Anesthesia and Head Placement (16)

On the day of the brain scan, study subjects were ushered into familiar carrying cages and transported to Mount Sinai Medical Center imaging facility in a dedicated animal transport van, with climate control. Following the imaging procedures, subjects returned on the same day to their home cages. Upon arrival at the scanner, animals were transported to a squeeze cage and following a brief restraint period, were rapidly given anesthetic agent intramuscularly. Saffan®, previously known as CT1341, is an injectable steroid anesthetic for use in cats and monkeys and as it minimizes motion artifact, relative to ketamine, was used to conduct the scans. Saffan®, administered at a dose of 16mg/kg, has two bioactive constituents; 12 mg/kg of alphaxalone and 4 mg/kg alphadolone acetate. Infrequently, animals necessitated subsequent doses of Saffan® (¼ initial dose) if there was evidence of motion during the scan secondary to diminished level of anesthesia. Subjects usually awakened within 20 minutes following completion of the one hour scan.

Once anesthesia was achieved, the monkey's head was positioned in a Styrofoam headrest inside a human knee coil, and the forehead was taped to the scanner, to further minimize movement artifact. Subjects were continuously monitored by pulse oximeter during anesthesia. Saffan® was non-toxic for all subjects, and did not produce respiratory depression. No other complications from the anesthesia or scan procedure occurred.

Diffusion Tensor Imaging (23)

DTI (Figure 1) data were acquired on a 3-T MRI Siemens Scanner. The protocol for the structural scans consisted of a three-plane sagittal localizer from which all other structural scans were prescribed. The following structural scans were acquired: Axial 3D-MPRage (TR=2500ms, TE=4.4ms, FOV=21cm, matrix size= 256×256, 208 slices with thickness=

0.82mm); Turbo spin echo T2-weighted Axial (TR=5380ms, TE=99ms, FOV=18.3cm × 21cm, matrix=512×448, Turbo factor=11, 28 slices, thickness=3mm skip 1mm); DTI using a pulsed-gradient spin-echo sequence with EPI-acquisition (TR=4100ms, TE=80ms, FOV=21cm, matrix=128×128, 24 slices, thickness=3mm skip 1mm, b-factor=1250 s/mm², 12 gradient directions, 5 averages). Raw DTI data were transferred to an off-line workstation for post-processing. In-house software written in *Matlab* v6.5 (The Mathworks Inc. Natick, MA) was used to compute the anisotropy and vector maps. The Fractional Anisotropy images were then converted to analyze format. *MEDx* v3.4.3 software (Medical Numerics Inc, Sterling, VA) was used to inspect and define ROIs on the FA images. Primary regions of interest (ROI) included the left and right anterior of the internal capsule. Secondary regions included posterior limbs of the internal capsule, left and right occipital lobe white matter and anterior and posterior corpus callosum.

Dentate Gyrus Neurogenesis, Hippocampal and Amygdala Volumetrics

Details for these measurements have been described previously (16, 22, 52). Dentate gyrus neurogenesis was measured at a mean age of 8.7 years whereas volumetric measurements were obtained concomitant to the DTI data (see Table 1).

Data analysis

Data were inspected for outliers and tested for normality of distribution.

A general linear model (Statistica 12.0) was used to test the hypothesis of anterior FA discordance and posterior FA concordance following ELS. The repeated measure included one within-subject factor – left versus right internal capsule white matter FA, which combined FA values of anterior and posterior limbs and occipital white matter (total number of values = 63). The between-subject variable was rearing group – VFD versus Non-VFD – and anterior versus posterior brain ROI was used as a categorical variable. FA of the corpus callosum was used as a single continuous predictor variable, with anterior corpus callosum representing the first 21 cases, posterior corpus callosum as the second 21 cases and then posterior corpus callosum repeated for a third tier of 21 cases. The design permitted determination of correlations between anterior structures (anterior corpus callosum and anterior limb of the internal capsule) and posterior structures (posterior corpus callosum with first posterior limb of the internal capsule and next with occipital white matter). Interactive effects included the term derived from a factorial ANOVA design rearing group*corpus callosum FA -- and a third triple interactive term of rearing group*corpus callosum (CC) FA*anterior-posterior (AP) gradient. A final control variable was entered coding for the three concordant relationships outlined above. The GLM was followed by univariate analyses examining each hemisphere separately. The hypothesis to be tested depended on significance of the triple interaction term in that the prediction of concordance between the limbs of the internal capsule and corpus callosum would differ as a function of rearing group and anterior/posterior regions. Significance on the repeated measures*rearing group*CC*AP term would suggest hemispheric effects of the triple interaction. Post-hoc testing was to be performed should the overall GLM prove significant and examined within region group, corpus callosum FA and a group*corpus callosum interaction using a factorial design ANOVA examining the prediction that FA concordance would be observed anteriorly

in Non-VFD reared versus VFD-reared subjects and that FA concordance would be observed posteriorly in VFD and not Non-VFD-reared subjects. A second post-hoc analysis examined within-group concordance between anterior and posterior regions using an ANOVA-RM. VFD subjects were hypothesized to exhibit relative FA concordance in posterior versus anterior regions and Non-VFD in anterior versus posterior regions.

Exploratory analyses examined the relationship of posterior cerebral white matter FA and frontal markers reflective of neuroplasticity – dentate gyrus neurogenesis and hippocampal volume – and a marker reflective of stress vulnerability – amygdala volume. A probability level of $p = 0.05$, two tailed was applied.

RESULTS

Determination of Covariates

There was no effect of weight, age, total brain volume or total white matter volume on DTI measures when including all subjects (Table 1). Distributions of primary variables were normal and no outliers were noted except for neurogenesis rates, which were logged. Since corpus callosum cross-sectional area was reduced in VFD- versus non-VFD reared subjects (16) we repeated key analyses controlling for this variable.

Capsular-Callosal Concordance for FA

For both left and right internal capsule white matter tracts, corpus callosum FA was generally positively predictive of hemispheric FA [$F_{1,56} = 11.78$; $p = 0.001$], an effect evident on the left [$F_{1,56} = 15.75$; $p = 0.0002$] and right [$F_{1,56} = 4.65$; $p = 0.035$] side. Validating the primary hypothesis of the current paper, a group $\times$ anteroposterior location $\times$ corpus callosum FA interactive was evident [$F_{1,56} = 4.24$; $p = 0.044$], an effect specifically evident in the left hemisphere [$F_{1,56} = 9.21$; $p = 0.004$] which was distinguishable from the right hemisphere [$F_{1,56} = 4.75$; $p = 0.03$].

The interactive effect in the left hemisphere was contributed to by a number of post-hoc effects. A marked anterior capsular-callosal concordance was noted in Non-VFD ($r = 0.96$; $p = 0.00002$) in contrast to an absence in VFD subjects [$r = -0.38$, $p = 0.21$; group $\times$ corpus callosum FA interactive effect: $F_{1,17} = 32.93$; $p = 0.00002$] (Figure 2). In VFD only, the absence of left ALIC-callosal concordance was in contrast to left concordance between PLIC and posterior corpus callosum FA ($r = 0.69$, $p = 0.014$) and occipital WM FA and posterior corpus callosum FA [$r = 0.62$, $p = 0.03$; $F_{1,32} = 10.61$; $p = 0.003$]. (see Figure 2). For Non-VFD, the marked anterior capsular-callosal concordance was lacking in posterior regions at a trend level [anteroposterior regions $\times$ corpus callosum FA, [$F_{1,23} = 3.05$; $p = 0.09$].

Posterior WM FA correlates

Because no systematic laterality differences were noted, mean PLICA FA and mean occipital WM FA were used. An exception was for left hippocampal neurogenesis where left posterior cerebral white matter FA structures were used as predictor variables.

Neurogenesis—Left PLICA FA correlated inversely with logged left hippocampal doublecortin counts, a marker of neurogenesis, in Non-VFD [$r = -.88$, $N = 5$, $p = 0.046$] but not in VFD [$r = 0.31$, $N = 9$, $p = 0.40$]. Thus, using a factorial ANOVA design, a trend for a group $\times$ log doublecortin effect was noted in the prediction of left PLICA FA [$F_{1,10} = 3.49$; $p = 0.09$]. Effect size determination revealed a partial $\eta^2 = 0.26$, almost twice the level required for a large effect size (0.14) (54).

Hippocampal Volume—No correlations were noted between posterior WM FA and right or left hippocampal volume. However, mean PLICA FA in Non-VFD positively predicted the right/left hippocampal volume ratio [$r = 0.75$, $N = 9$, $p = 0.019$], whereas in VFD, mean PLICA FA inversely predicted the ratio [$r = -0.61$, $N = 11$, $p = 0.045$] (Figure 3).

VFD exhibited an increased right/left hippocampal ratio when adjusting for mean PLICA FA compared to VFD [(VFD mean (SE) = 1.11 (0.02) versus Non-VFD mean (SE) = 1.01 (0.03): $F_{1,16} = 15.03$; $p = 0.001$]. The groups therefore differed in the manner in which mean PLICA FA predicted right/left hippocampal volume ratio [rearing group $\times$ mean PLICA FA interaction: $F_{1,16} = 11.99$; $p = 0.003$]. No effects were noted for occipital WM FA.

Amygdala Volume—Mean occipital FA directly predicted mean amygdala volume in Non-VFD [$r = .88$, $N = 9$, $p = 0.001$]. By contrast, no relationship was observed in VFD between mean occipital FA and mean amygdala volume [$r = 0.09$; $N = 11$, $p = 0.77$]. Although the factorial ANOVA entailing group $\times$ mean occipital FA was not significant, within Non-VFD subjects there was a significant regional location mean WM FA $\times$ mean amygdala volume interaction [$F_{1,21} = 6.75$; $p = 0.005$] in that whereas mean occipital WM FA directly predicted mean amygdala volume, the relationship between mean amygdala volume and mean ALIC FA was inverse at a trend level [$r = -0.60$; $N = 9$, $p = 0.08$]. Mean PLICA FA directly predicted mean amygdala volume but this effect was not significant [$r = 0.56$; $N = 9$, $p = 0.12$].

Since data from previous cohorts revealed increases in BMI and metabolic syndrome-like measures (21, 55), in the current study controlling for body mass did not affect the significance of the results nor was body mass a significant covariate. Total brain volume, a necessary covariate in volumetric studies(16), did not change the significance of the results when introduced as a control variable. Nor was it a significant covariate.

DISCUSSION

The data of the current study imply, in a preliminary fashion, that concordance of WM FA, a putative marker of homogenous WM neuroplastic effects, varies by virtue of exposure to ELS, by anterior versus posterior locations and an interaction of ELS exposure and anteroposterior location. Thus, in frontal areas, the FA concordance between ALIC and anterior corpus callosum (ACorpusC) is markedly evident in Non-VFD subjects and absent, to a significant degree, in VFD subjects. The absence of left anterior concordance in VFD subjects is in contrast to significant posterior FA concordance between both PLICA and posterior corpus callosum (PCorpusC) and occipital WM and PCorpusC. The frontal FA concordance present in Non-VFD was absent, at trend levels, in posterior regions. The

overall effect appears asymmetric, being significantly more prominent in the left versus right cerebral hemisphere. The data of the current study therefore raise the possibility that disruption of the homogeneity of frontal white matter integrity by ELS, a precursor for human mood and anxiety disorders (2), may contribute, in part, to a state of white matter-mediated global prefrontal dysconnectivity invoked in severe psychiatric disorders which follow on impairment in distributed neural networks (26). This hypothesis receives support from the observation that the frontal regions of interest, the ALIC and ACorpusC both communicate, albeit through distinct pathways, with the prefrontal cortex (23, 48). As abnormal neuroplasticity is posited to underlie the impairment of distributed neural networks (32), disruptions of the homogeneity of white matter integrity, attributable to neurotrophic modifications (46), should be considered as a potential contributory factor to prefrontal global dysconnectivity. In fact, human childhood neglect has been demonstrated to exhibit prefrontal dysconnectivity independent of pathology associated with MDD (28). We have, as discussed above, shown that mean FA of the anterior limbs of the internal capsule correlated inversely with right and left amygdala volume, a marker of early life stress, specifically in VFD versus Non-VFD subjects (22). In addition, elevations of CSF 5-HIAA, a putative indicator of reduced serotonin neurotransmission, inversely predicted mean FA of the anterior limbs of the internal capsule but only in VFD-reared versus normally reared subjects (20).

Additionally, correlates of posterior WM FA were evident for frontal neurotrophic markers, which were divergent to the directionality observed for frontal FA and were generally inverse, although these effects were primarily evident in Non-VFD and not VFD subjects. A marked inverse correlation was noted between left PLICA FA and left hippocampal neurogenesis, as reflected by dentate gyrus doublecortin counts, in Non-VFD subjects, but was absent in VFD subjects. Although these two correlations were only distinguishable at a trend level, the effects size distinguishing them was evident at almost twice that required for a large effect size. Thus, the theme of posterior FA varying inversely with an anterior marker of neuroplasticity was evident, but noted only in the subjects not exposed to ELS. One interpretation of this observation is that ELS disrupts not only frontal concordance but also posterior (yet inverse) FA concordance.

For hippocampal volume, no effects were observed for right, left or mean PLICA FA. However, right > left hippocampal volume asymmetry (right/left) was increased in VFD versus Non-VFD subjects, consistent with previous reports, where reductions in left hippocampal volume in VFD subjects versus controls had been observed (16). In Non-VFD, the relationship between hippocampal volume asymmetry and mean PLICA FA was positive. In other words, consistent with the overall hypothesis, greater posterior FA was associated with a less favorable neurotrophic status (right > left hippocampal volume) in anterolateral regions [discussed in (56)] but only in Non-VFD subjects. In VFD subjects, those subjects exhibiting the greatest right > left hippocampal volume asymmetry had the lowest mean PLICA FA (see figure 3). Thus, VFD subjects exhibited a relationship opposite to that observed in Non-VFD, further emphasizing the disruptive effects of ELS on concordant relationships for both anterior and posterior structures.

Consistent with the notion of posterior activity directly predicting stress markers, mean occipital FA markedly predicted mean amygdala volume (22) in a positive fashion although the absent relationship in VFD was not significantly distinguishable from Non-VFD. The within-Non-VFD direct relationship between mean occipital WM FA and mean amygdala volume was distinguishable from a trend inverse relationship between mean ALIC FA and mean amygdala volume. Thus, again, consistent with the notion that anterior white matter FA was concordant with markers of neuroplasticity, posterior white matter FA was directly correlated with markers of stress inversely related to neuroplasticity (20). Although left posterior WM concordance was specifically evident in VFD, inverse relationships between posterior WM FA and markers of neuroplasticity were specifically evident in Non-VFD. The latter observation suggests an additional alteration following ELS: loss of an inverse posterior-anterior relationship.

The nonhuman primate white matter FA findings have previously supported the notion that early life stress of the VFD form reduces ALIC FA (47). The findings of the current study, however, support the view that emotional integrity of the maternal-infant attachment process is critical to the normative synchronous development of frontal white matter tracts and also disrupts an inverse relationship between posterior white matter tracts and anterolateral markers of neuroplasticity (11, 57).

The degree to which frontal white matter tract FA may serve as a potentially informative indicator of the general neurotrophic status of brain regions implicated in human anxiety and mood disorders is of interest. One hypothesis is that early life stress interacts with vulnerable genotypes to produce persistent suppression of neurotrophic growth factors (58). BDNF, for instance, increases myelin basic protein production by promoting oligodendrogenesis, thereby facilitating CNS myelination.(59), (60), (61). The presence of errant posterior capsular-callosal concordance for FA in VFD-reared subjects (Figure 2) raises the possibility that one aspect of the VFD-phenotype is enhanced posterior homogeneity of myelin production. The putative consequences of errant posterior white matter FA concordance for frontal lobe function and affective regulation has not, to our knowledge, been investigated.

Several caveats and limitations warrant mention. The DTI scans of the current study were performed only in male subjects, limiting generalizability to females, in whom anxiety and mood disorders are most common (62). Previous studies have noted regional differences of fractional anisotropy within the corpus callosum between men and women (63). Of note, however, neuropsychiatrically healthy men and women, spanning the adult age range, show a similar pattern of variation in regional white matter coherence. (64) Although males obviate potential variation introduced by phase of the female monkey menstrual cycle, future studies with a larger number of subjects should include females. Frontal findings were exclusively evident in the left hemisphere to a significant degree, a hemisphere shown previously to be preferentially vulnerable to VFD exposure (16) and also to play a role in the elaboration of positive affect (56). Thus, future studies should bear in mind the potential role of cerebral WM FA asymmetry in prefrontal global dysconnectivity.

Since data from previous cohorts revealed increases in BMI and metabolic syndrome-like measures(21, 55), in the current study controlling for body mass did not affect the

significance of the results. Total brain volume, a necessary covariate in volumetric studies(16), did not change the significance of the results when introduced as a control variable. Thus, the concern of these confounds are addressed.

The statistical issue is raised as to whether the use of an “empirical null hypothesis” should be used when multiple measures were simultaneously gathered. However, the empirical null hypothesis is viewed to be relevant at $N > 100$ (65). We therefore employ the “theoretical null hypothesis” as currently used in the manuscript. Moreover, as the results were not corrected for multiple comparisons, the results might be misleading.

The issue is raised how the degrees of freedom was greater than the total number of cases. Brain areas and scan parameters were not used to determine total number of cases or degrees of freedom. Degrees of freedom were derived from the results of the statistical package used (Statistica 12.0), and therefore did not inflate sample size. The number of degrees of freedom is generally calculated based on the design. Therefore we had analyses where the number of degrees of freedom was greater than the total number of cases.

Another consideration was that the neurogenesis studies were performed at a mean age of 8.7 years whereas the imaging studies were performed at an approximate age of five years. It would have been ideal that these measures were obtained contemporaneously but the neurogenesis relationships were an ancillary hypothesis.

We therefore provide preliminary evidence for the view that a concordant relationship between left anterior capsular-callosal FA may become discordant, providing a mechanism, at least in part, for prefrontal brain dysconnectivity. This view rests on the premise that between-region concordance of FA could conceivably reflect neuroplastic homogeneity, facilitating orderly distribution of brain networks, whereas neuroplastic inhomogeneity would facilitate dysconnectivity and negative affective states. Evidence was also provided, in an exploratory fashion, of an anterior/posterior WM FA divergence as relates to frontal structures reflective of neuroplasticity. Further studies are required to test these hypotheses.

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Highlights

- neuroimaging studies report global brain dysconnectivity (GBD) in mood disorders
- integrity of white matter (WM) is examined in the context of brain dysconnectivity
- early life stress (ELS) induces alterations in WM volumetrics and integrity
- exposure to ELS exhibited impairments in concordance of WM integrity
- ELS may contribute to GBD through WM concordance impairment

Figure 1. Diffusion Tensor Imaging of the Nonhuman Primate Using a 4-T MRI Scan – Voxel Placement

DTI data were acquired on a 3-T MRI Siemens Scanner. The protocol for the structural scans consisted of a three-plane sagittal localizer from which all other structural scans were prescribed. Raw DTI data were transferred to an off-line workstation for post-processing. In-house software written in *Matlab* v6.5 (The Mathworks Inc. Natick, MA) was used to compute the anisotropy and vector maps. The Fractional Anisotropy images were then converted to analyze format. *MEDx* v3.4.3 software (Medical Numerics Inc, Sterling, VA) was used to inspect and define ROIs on the FA images. Primary regions of interest (ROI) included the left and right anterior limbs of the internal capsule. Secondary regions included posterior limbs of the internal capsule, left and right occipital lobe white matter and anterior and posterior corpus callosum.

Figure 2. Categorized Scatterplot For Left FA Concordance Between Anterior Corpus Callosum and Anterior Limb of the Internal Capsule and Between Posterior Corpus Callosum and between Posterior Corpus Callosum and both Posterior Limb of the Internal Capsule and Occipital White. Matter using Rearing Group and Anterior-Posterior regions as Categorized Variables

Validating the primary hypothesis of the current paper, a group $\times$ anteroposterior location $\times$ corpus callosus FA interactive was evident [$F_{1,56} = 4.24$; $p = 0.044$], an effect specifically evident on the left [$F_{1,56} = 9.21$; $p = 0.004$] versus right side [$F_{1,56} = 4.75$; $p = 0.03$]. The interactive effect on the left was contributed to by a number of post-hoc effects. A marked anterior capsular-callosal concordance was noted in Non-VFD in contrast to an absence in VFD subjects [group $\times$ corpus callosus FA interactive effect [$F_{1,17} = 32.93$; $p = 0.00002$]]. In VFD only, the absence of left ALIC-callosal concordance was in contrast to left concordance between posterior corpus callosus FA and both PLIC and occipital WM concordance [$F_{1,32} = 10.61$; $p = 0.003$]. For Non-VFD, the marked anterior capsular-callosal concordance was lacking in posterior regions at a trend level [anteroposterior regions $\times$ corpus callosus FA, [$F_{1,23} = 3.05$; $p = 0.09$]]. The lack of frontal and presence of errant posterior capsular-callosal concordance for FA in VFD-reared subjects versus controls raises the question whether one aspect of the VFD-phenotype is disrupted anterior homogeneity of myelin production, and synchrony of posterior myelin integrity with putative consequences for affective regulation.

Figure 3. Categorized Scatterplot of Posterior Limb of the Anterior Limb Mean FA and Hippocampal Volume Asymmetry

No correlations were noted between posterior WM FA and right or left hippocampal volume. However, mean PLICA FA exhibited differing relationships to Hippocampal Volume Asymmetry (Right/Left Ratio) as a function of ELS exposure. Mean PLICA FA, however, in Non-VFD directly predicted the right/left hippocampal volume ratio [$r = 0.75$, $N = 9$, $p = 0.019$] whereas in VFD, mean PLICA FA inversely predicted the ratio [$r = -0.61$, $N = 11$, $p = 0.045$].

VFD exhibited an increased right/left hippocampal ratio when adjusting for mean PLICA FA compared to VFD [(VFD mean (SE) = 1.11 (0.02) versus non-VFD mean (SE) = 1.01 (0.03); $F_{1,16} = 15.03$; $p = 0.001$]. The groups therefore differed in the manner in which mean PLICA FA predicted right/left hippocampal volume ratio [rearing group $\times$ mean PLICA FA interaction: $F_{1,16} = 11.99$; $p = 0.003$].

Table 1

Means and Standard Deviations of Independent Variables

	VFD	Non-VFD	t-value	p-value
N	12	9	(df =19)	
AGE (months)				
Mean (SD)	59.95±32.30	66.26±31.70	0.45	0.66
Weight (KG)				
Mean (SD)	4.85±1.31	5.15±1.78	0.44	0.66
Brain Volume (mm³)				
Mean (SD)	81477.61±6201.15	77189.32±5121.79	-1.69	0.11
White Matter Volume (mm³)				
Mean (SD)	3978.06±505.84	3969.14±483.25	-0.04	0.97