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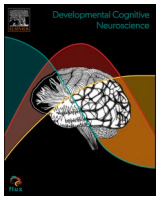

Altered associations between white matter structure and psychopathology in previously institutionalized adolescents

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ABSTRACT

Previously institutionalized adolescents show increased risk for psychopathology, though placement into high-quality foster care can partially mitigate this risk. White matter (WM) structure is associated with early institutional rearing and psychopathology in youth. Here we investigate associations between WM structure and psychopathology in previously institutionalized youth. Adolescent psychopathology data were collected using the MacArthur Health and Behavior Questionnaire. Participants underwent diffusion MRI, and data were processed using fixel-based analyses. General linear models investigated interactions between institutionalization groups and psychopathology on fixel metrics. Supplementary analyses also examined the main effects of psychopathology and institutionalization group on fixel metrics. Ever–Institutionalized children included 41 randomized to foster care (Mage=16.6), and 40 to care-as-usual (Mage=16.7)). In addition, 33 participants without a history of institutionalization were included as a reference group (Mage=16.9). Ever–Institutionalized adolescents displayed altered general psychopathology–fixel associations within the cerebellar peduncles, inferior longitudinal fasciculi, corticospinal tract, and corpus callosum, and altered externalizing–fixel associations within the cingulum and fornix. Our findings indicate brain–behavior associations reported in the literature may not be generalizable to all populations. Previously institutionalized youth may develop differential brain development, which in turn leads to altered neural correlates of psychopathology that are still apparent in adolescence.

1. Introduction

The psychological deprivation often associated with institutional rearing has consistently been shown to impact lifelong behavioral outcomes; for example, previously institutionalized youth face increased risk for clinical (Humphreys et al., 2020) and transdiagnostic psychopathology (Wade et al., 2018). Findings from the Bucharest Early Intervention Project (BEIP) have shown that random assignment to high-quality foster care can partially mitigate this risk of psychopathology (Humphreys et al., 2020; Wade et al., 2018), possibly by altering neurodevelopment in this population (Wade et al., 2022). However, the structural neural correlates associated with this population's increased risk for psychopathology remain understudied.

Individuals who experience early deprivation exhibit altered white matter (WM) microstructure, as reported by diffusion tensor imaging (DTI) studies, showing both increased and decreased DTI metrics compared to controls (Banihashemi et al., 2021; Bick et al., 2015; Govindan et al., 2010; Olson et al., 2015; Sheridan et al., 2022). There are further inconsistencies in findings across studies, with one recent study of previously institutionalized young adults indicating smaller macrostructural WM volume, without the presence of microstructural tensor metric alterations (Mackes et al., 2022). The discrepancies may result from

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failures of some DTI methods to properly account for complex fiber architecture (such as crossing fibers; Tournier et al., 2011). Fixel-based analysis (FBA) provides a more sensitive measure of WM structure by quantifying diffusion characteristics of specific fiber populations within voxels (Raffelt et al., 2017). FBA quantifies microstructure and macrostructure separately, and then combines these two metrics, to provide a more complete measure of total intra-axonal volume in WM tracts. In recent years, studies use FBA methods to relate psychopathology to WM microstructure and macrostructure (Burley et al., 2021; Gilchrist et al., 2023; Grazioplene et al., 2020), replicating and extending DTI findings of similar associations (Sagarwala and Nasrallah, 2020).

Previous analyses from the BEIP show group differences between adolescents with a history of institutionalization and those raised in family homes, in both WM structure of specific WM tracts and grey matter structure of the inferior frontal gyrus and anterior cingulate cortex (Sheridan et al., 2022). Analyses also revealed associations between *increased* anterior cingulate cortex thickness and elevated psychopathology in this sample (Sheridan et al., 2022). In contrast, similar investigations in non-institutionalized populations report associations between elevated psychopathology and *decreased* cortical thickness (Iwashiro et al., 2012; Xiao et al., 2015) and volume (Hu and Dolcos, 2017) in the frontal lobe. These opposite results may reflect equifinality, which refers to the observation that a variety of pathways could lead to similar outcomes, and therefore, different populations may develop similar phenotypes through differential pathways and processes (Cicchetti and Rogosch, 1996; Humphreys and Zeanah, 2015). Studies in other populations reveal other examples of equifinality, such as in adolescents born prematurely, where associations between psychopathology and WM structure differ when compared to full-term controls: while control adolescents exhibit a negative association between tract micro- and macro-structure and psychopathology, premature subjects do not display such associations (Gilchrist et al., 2023). Exploring moderating effects of early deprivation on brain–behavior associations may reveal neural correlates of psychopathology unique to previously institutionalized individuals. Indeed, such moderating effects of early adversity manifest in the association between limbic functional activity and both depression (Rodman et al., 2019) and anxiety (Silvers et al., 2017). Here we examine the moderating effects of early institutionalization on the relations between WM structure and psychopathology using state-of-the-art fixel-based analysis.

In the current study we explore the impact early institutionalization has on the neural correlates of psychopathology, using data from BEIP. The BEIP recruited young children who had been abandoned soon after birth and placed in large, impersonal institutions in Bucharest, Romania (ever-institutionalized group; EIG), and then randomized into a foster care group (FCG) or to a care-as-usual group (CAUG). An additional comparison group of never-institutionalized children (NIG) also were recruited from the community. All groups were followed up at multiple timepoints during childhood and adolescence (Nelson et al., 2023), and prior analyses have identified increased risk for psychopathology in those with a history of institutionalization, especially in those with prolonged institutionalization (CAUG), who showed higher rates of meeting criteria for any psychiatric disorder, as well as higher symptom counts of internalizing, externalizing, attention deficit/hyperactivity, and substance use disorders, at 12 and 16 years (Humphreys et al., 2015, 2020). Adolescent psychopathology has also been quantified through latent factors created previously within this cohort: general psychopathology (P factor) and residual internalizing and externalizing symptoms (Wade et al., 2018). Group differences are present in the developmental trajectories of these factors, and by age 16 years, CAUG showed significantly increased P factor and residual externalizing symptoms compared to those raised in either family homes or foster care (Wade et al., 2018). Additionally, as mentioned above, BEIP group differences in WM structure have been reported in specific WM tracts, including the anterior thalamic radiation, uncinate fasciculus, and superior longitudinal fasciculi (Sheridan et al., 2022).

Current analyses aimed to replicate and expand on prior DTI findings of group differences in WM structure, using FBA. We identified whole-brain group-differences in fixel metrics as well as region-of-interest analyses within specific WM tracts shown to exhibit structural alterations in previously institutionalized adolescents (Sheridan et al., 2022). Group comparisons explored both the effects of early random assignment to foster care (FCG vs CAUG), as well as early institutionalization (EIG vs NIG). Second, whole-brain analyses explored associations between fixel metrics and psychopathology factors in all participants. Finally, the current study builds on previous findings of group differences in both brain (Sheridan et al., 2022) and behavioral outcomes (Wade et al., 2018) by exploring group differences in brain–behavior associations. To do this, we examined the interaction between institutionalization group and psychopathology on WM structure across the whole brain. Assuming differential pathways to psychopathology between groups experiencing varying levels of early deprivation, we expected to find a moderating effect of institutional rearing on the relations between structural connectivity and psychopathology. Specifically, adolescents growing up in family homes would be expected to display brain–behavior associations similar to those reported in prior analyses, including negative associations between widespread fiber micro- and macrostructure and psychopathology (Burley et al., 2021; Gilchrist et al., 2023; Grazioplene et al., 2020), while those with a history of institutionalization would show differential brain–behavior associations.

2. Methods

2.1. Participants

Participants were recruited as part of the BEIP, a longitudinal study of children raised from early infancy in institutions in Bucharest, Romania (Zeanah et al., 2003). Children's legal guardians provided signed informed consent (children age 8 years and older provided written or verbal assent). Ethics approval was obtained from the institutional review boards of the three principal investigators' universities and from the local Commissions on Child Protection in Bucharest. One hundred and thirty-six children (6–30 months old) were recruited from six institutions for young children (EIG). Between 6 and 33 months, half the children recruited from institutions were randomized to a high-quality foster-care intervention (FCG), and the other half were exposed to more prolonged institutional care (CAUG). An age-matched control group was recruited from public pediatric clinics (NIG).

At 16 years, 115 participants were followed up for neuroimaging and behavioral data collection (n=41 CAUG; n=41 FCG; n=33 NIG). For further information on retention rates in the BEIP study, see Sheridan et al. (2022). One participant whose data had been collected did not have usable diffusion MRI data and was excluded from subsequent analyses (more information can be found in Diffusion MRI Processing). The current study reports on data collected at 16 years, and cohort characteristics are described in Table 1. Neither age nor sex were significantly different among the three groups ($p > 0.05$).

2.2. MRI acquisition

Structural MRI were acquired at Santador Hospital (Bucharest, Romania) on a Siemens Magnetom 1.5 T Syngo system. Structural images were obtained using an MPRAGE sequence (TE = 3.5 ms, T1 = 1100 ms, flip angle = 7192 slices with isometric voxels of 1 mm^3, TR = 2530, acceleration factor 2 (using GRAPPA) with an eight-channel head coil.

Diffusion-weighted images were acquired in 30 directions, with the following scan parameters: 29 b=1000 and 1 unweighted (b=0) scans, TE/TR = 88 ms/8500 s, partial Fourier coverage of 7/8, an acceleration factor of 2, 216-mm field of view, and voxel size of 2 mm^3.

Table 1
Cohort Characteristics.

	All subjects (n=114)	EIG		NIG (n=33)	Group difference (p)
		CAUG (n=40)	FCG (n=41)		
Females (%)	49.12	45.00	51.22	51.52	0.571
Age at assessment, mean (SD)	16.72 (0.51)	16.7 (0.49)	16.6 (0.53)	16.9 (0.48)	0.107

CAUG = Care As Usual Group; EIG = Ever Institutionalized Group; FCG = Foster Care Group; NIG = Never Institutionalized Group; SD = standard deviation.

2.3. Structural MRI processing

Cortical reconstruction and volumetric segmentation were performed with FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu), further information on processing can be found in (Sheridan et al., 2022). Intracranial volumes were calculated.

2.4. Diffusion MRI processing

Diffusion data were preprocessed with DTIPrep (Oguz et al., 2014). Preprocessing steps included detection and removal of "venetian blind" artifacts, eddy current and motion artifact correction. Corrupted diffusion-weighted volumes were then removed, and only datasets that retained >80 % of volumes were used for further analyses. One CAUG dataset was excluded, leaving a total of 114 useable DWI datasets (40 CAUG datasets).

Fixel-based processing steps were conducted using MRtrix3 software (version 3.0.3), according to procedures outlined in the MRtrix3 documentation (Raffelt et al., 2017). Briefly, images underwent bias field correction and global intensity normalization. Average WM single-shell response function was calculated, and images were upsampled to voxel size 1.25 mm isometric. Fiber Orientation Distribution (FOD) was calculated using constrained spherical deconvolution (CSD), and a study-specific unbiased FOD template was created with 40 participants that were selected to represent the full sample. The sub-group used to create this template included 14 CAUG, 15 FCG, and 10 NIG participants. Group comparisons between those who were, and were not, included in this sub-group revealed no significant differences in terms of age, sex, institutionalization group, and psychopathology (including P factor, externalizing, and internalizing symptoms) (p values > 0.132).

Individual FOD images were registered to a FOD template, which was then used to create a fixel mask, defining fixels for which statistical analyses were performed on. FBA produced three metrics of WM structure: a) Fiber Density (FD) measures microstructural intra-axonal volume; b) Fiber Cross-section (FC) measures the macrostructural cross-section of a WM tract; c) Fiber Density & Cross-section (FDC), a combination of FD and FC, is a measure the total intra-axonal volume within a WM tract (Dhollander et al., 2021). Per-subject fixel images for all three metrics were computed, and a whole-brain tractogram was generated, subsequently used to inform statistical analyses.

For region-of-interest analyses, individual WM tracts were delineated using TractSeg (Wasserthal et al., 2018), which computed binary masks and tractograms of chosen tracts. WM tracts were chosen based on previous analyses (Sheridan et al., 2022): anterior thalamic radiation, superior longitudinal fasciculus, uncinate fasciculus, and genu/forceps minor.

2.5. Psychopathology

Psychopathology data were collected from caregiver and teacher reports using the MacArthur Health and Behavior Questionnaire (HBQ), shown to display test-retest and inter-rater reliability (Essex et al., 2002). Teacher and caregiver reports were standardized and combined into a composite score to reduce rater bias. As part of a previous investigation, bifactor models were fit to examine latent structure of psychopathology, and factor scores were generated for general psychopathology (P factor) and residual externalizing and internalizing symptoms. The P factor captured common variance across all eight psychopathology domains, and the remaining two factors captured residual variance within their own domains. The current analysis used all three factors at 16 years. More details on methods for factor estimation can be found at Wade et al. (2018).

2.6. Statistical analyses

Fixel-based statistical analyses were performed using connectivity-based fixel enhancement, a technique employing the general linear model (GLM), which provides a permutation-based, family-wise error (FWE) corrected p-value for every fixel in a template. All models controlled for age and sex, and models for FC & FDC additionally controlled for ICV, as is suggested by Smith et al. (2019).

GLMs investigated the interaction between BEIP groups and psychopathology (P factor, externalizing, and internalizing) on fixel metrics (FD, FC, and FDC). Group comparisons included FCG vs CAUG, examining the impact of random assignment to foster care intervention. Following this, analyses compared EIG to NIG, or the impact of exposure to institutionalization. Average fixel metrics within significant group clusters were extracted and brain–behavior associations were visualized in RStudio.

Supplementary analyses examining the main effects of institutionalization group on fixel metrics, both whole-brain and region-of-interest, were conducted to replicate previous analyses of group differences in DTI metrics (Sheridan et al., 2022). For replication analyses, fixel-based analyses were performed within masks of chosen WM tracts. Finally, supplementary analyses were performed to examine the main effects of psychopathology on fixel metrics.

3. Results

3.1. Institutionalization group comparisons

No significant differences were found in whole-brain analyses of any fixel metric (FD, FC, and FDC) in either group comparisons (CAUG vs FCG; EIG vs NIG).

Results from region-of-interest analyses are found in the Supplemental Materials (Table S1) and replicate previous DTI group differences (Sheridan et al., 2022), specifically within the anterior thalamic radiation, superior longitudinal fasciculus, uncinate fasciculus, and forceps minor.

3.2. Fixel-wise associations with psychopathology

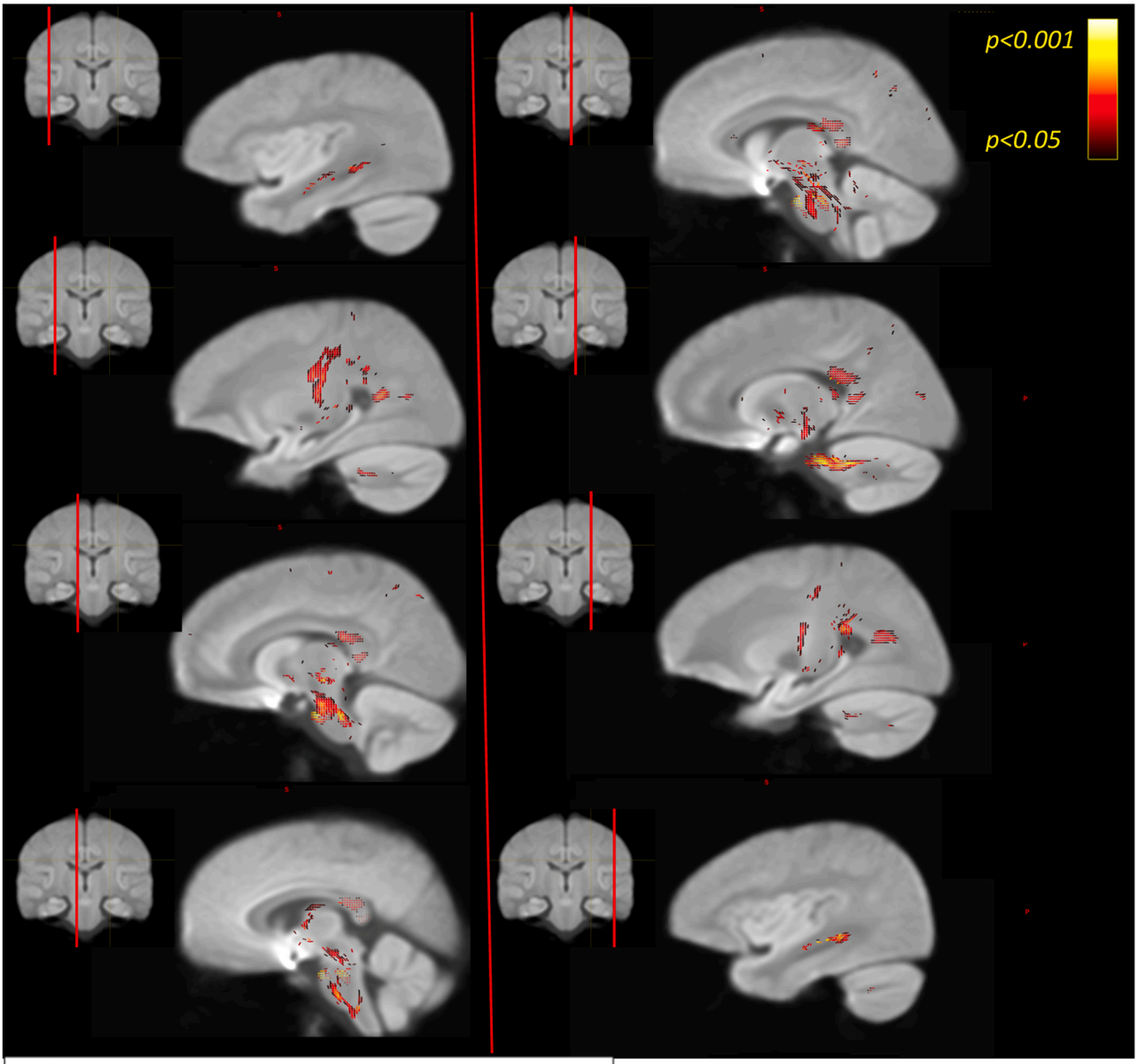
Results from brain-wide associations with psychopathology can be found in Supplementary Materials, Figure S1. We found widespread associations between P factor and FDC, as well as between residual externalizing symptoms and both FDC & FD. No associations between residual internalizing symptoms and fixel metrics were observed.

3.3. Group differences in brain–behavior associations

3.3.1. P factor

No significant group differences were found between FCG and CAUG in associations between fixel metrics and P factor.

a.



b.

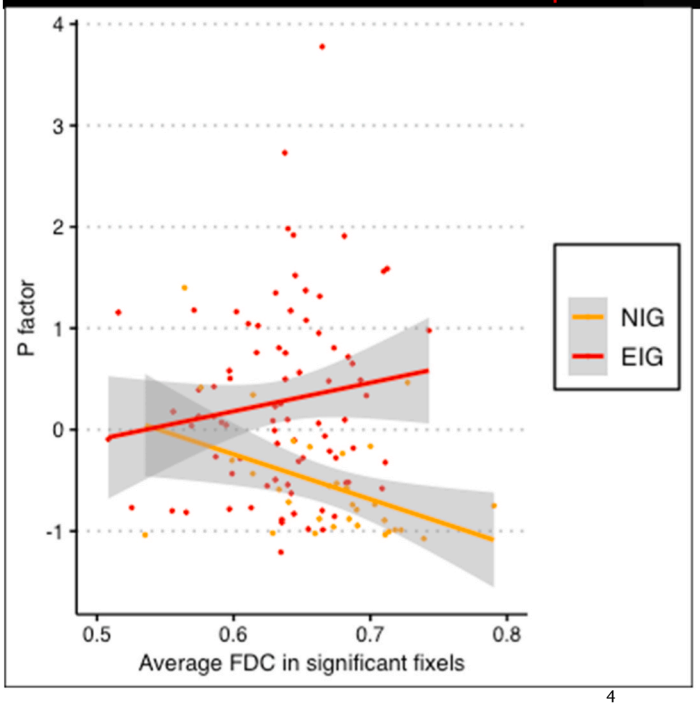


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Fig. 1. a. Fixels with significant differences in FDC–P factor associations between EIG & NIG, in population-specific template space. b. Post-hoc visualization of group differences in associations between P factor and average FDC of significant fixels: NIG show a negative association between FDC and P factor, such that elevated general psychopathology is associated with decreased fiber micro- and macrostructure.

Significant differences in FDC–P factor associations were found between EIG and NIG. WM tracts with significant differences included corticospinal tract, cerebellar peduncles, inferior longitudinal fasciculus, fornix, and forceps major (Fig. 1a). Post-hoc visualization of this effect demonstrated a negative association between FDC in significant fixels and P factor in NIG, such that elevated general psychopathology correlated with decreased FDC. No such association between FDC and P factor was found in EIG (Fig. 1b).

[The electronic version of this publication includes a video of results in 3D, on whole-brain template-derived tractogram. Video 1 shows significant group*P factor interactions.]

Five outliers were found in the P factor variable. Repeated analyses with outliers removed revealed similar significant findings ($p < 0.03$).

3.3.2. *Externalizing*

No significant differences were found between FCG and CAUG in associations between fixel metrics and residual externalizing symptoms.

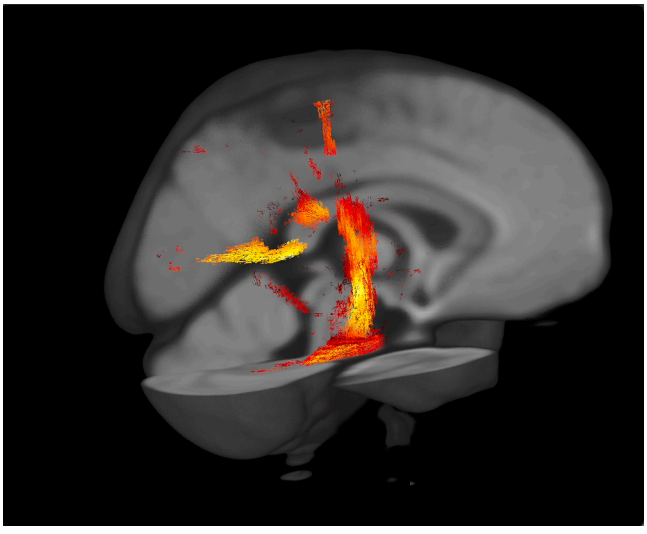
Significant differences in FC–externalizing associations were found between EIG and NIG within the cingulum, localized to the right anterior cingulum (Fig. 2a). Post-hoc visualization of this effect demonstrated a negative association between FC and residual externalizing symptoms in NIG, such that elevated externalizing symptoms correlated with decreased cingulum FC. No such association between cingulum FC and externalizing was found in EIG (Fig. 2b).

Significant differences in associations between FC and externalizing symptoms were also observed within the fornix (Fig. 2c). Post-hoc visualization of this effect demonstrated a positive association between FC and residual externalizing symptoms in NIG, such that elevated externalizing symptoms correlated with increased fornix FC. No such association between fornix FC and externalizing was found in EIG (Fig. 2d).

[The electronic version of this publication includes a video of results in 3D, on whole-brain template-derived tractogram. Videos 2, 3 show significant group*externalizing interactions.]

3.3.3. *Internalizing*

No significant group differences were found in associations between fixel metrics and residual internalizing symptoms.



Video 1. A video clip is available online. Supplementary material related to this article can be found online at doi:10.1016/j.dcn.2024.101440.

4. Discussion

In the current study, previously institutionalized adolescents displayed differential associations between WM structure and psychopathology, compared to adolescents without a history of institutionalization. Specifically, adolescents growing up in family homes displayed a negative association between general psychopathology and widespread WM structure, while their residual externalizing symptoms associated positively with decreased cingulum and increased fornix macrostructure. These patterns were not observed in individuals exposed to early institutionalization, suggesting they are not universally optimal neural profiles. Studies of humans and non-human primates demonstrate detrimental effects of early life deprivation on WM structure (Hanson et al., 2013; Howell et al., 2019). This may lead to the development of differential optimal brain development in those experiencing early deprivation, that is dependent on an individuals' early environment (Ellwood-Lowe et al., 2021).

Group effects of differential associations between WM structure and general psychopathology in adolescents with a history of institutionalization were found within the cerebellar peduncles, inferior longitudinal fasciculi, corticospinal tract, and the isthmus and splenium of the corpus callosum. Previous analyses have observed associations between elevated psychopathology and decreased microstructure within these corticocortical and corticocerebellar WM tracts (Jenkins et al., 2016; Neumann et al., 2020; Romer et al., 2018). Our findings contribute to the literature by suggesting ways in which brain–behavior associations may vary across social contexts. Specifically, in WM regions where we observed expected patterns in the never-institutionalized group, the previously institutionalized group exhibited few associations between WM structure and psychopathology. This suggests that the neural pathways associated with psychopathology in previously institutionalized individuals differ from those related to psychopathology in other populations. Additionally, a recent study showed the dynamic characteristics of associations between psychopathology and structural connectivity over childhood and adolescence (Grazioplene et al., 2022). Thus, early institutionalization may disrupt commonly observed developmental trajectories reflected in such brain–behavior associations, as suggested by previous observations in this sample on the development of grey matter (Sheridan et al., 2022).

Differential associations between WM structure and residual externalizing symptoms were localized to the cingulum and fornix. Within the cingulum, never-institutionalized adolescents, unlike previously institutionalized individuals, exhibited an association between decreased cingulum macrostructure and elevated residual externalizing symptoms. The cingulum connects the cingulate cortex to limbic structures, including the amygdala and hippocampus. It undergoes substantial and prolonged maturation well into early adulthood (Lebel and Beaulieu, 2011), and is important for the development of attention and cognitive control (Bubb et al., 2018), vital for emotional and behavioral regulation. Previous investigations have indicated associations between cingulum microstructure and externalizing symptoms in children and adolescents, using both DTI (Andre et al., 2020; Menks et al., 2017) and FBA (Grazioplene et al., 2020). Further, cingulum structure is altered in previously institutionalized individuals, exhibited as both decreased fractional anisotropy (a microstructural DTI metric) in children (Kumar et al., 2014) and as decreased macrostructural volumes in young adults (Mackes et al., 2022). The current results extend existing literature by demonstrating that typical associations between cingulum structure and externalizing symptoms are not observed in previously institutionalized adolescents.

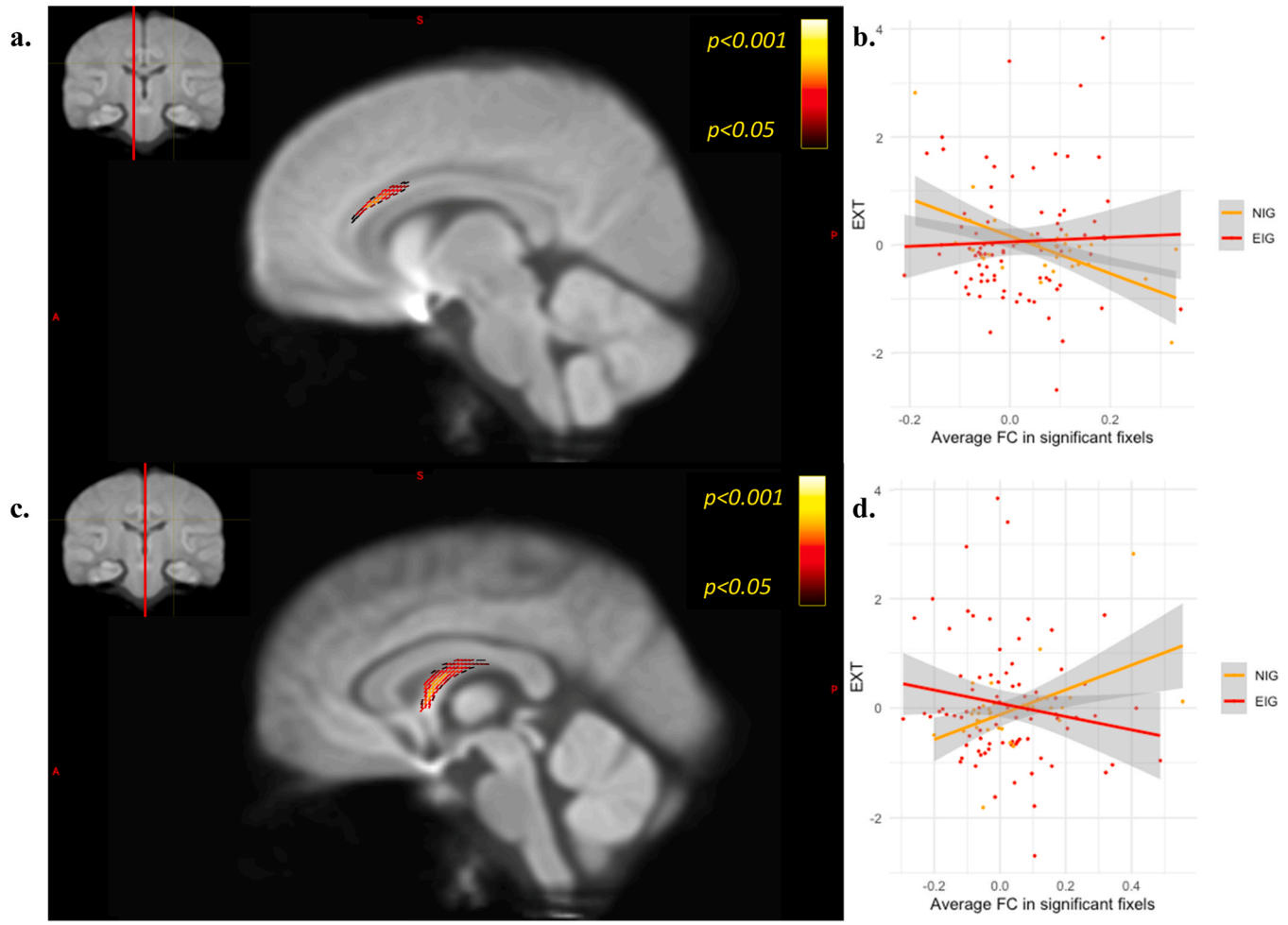
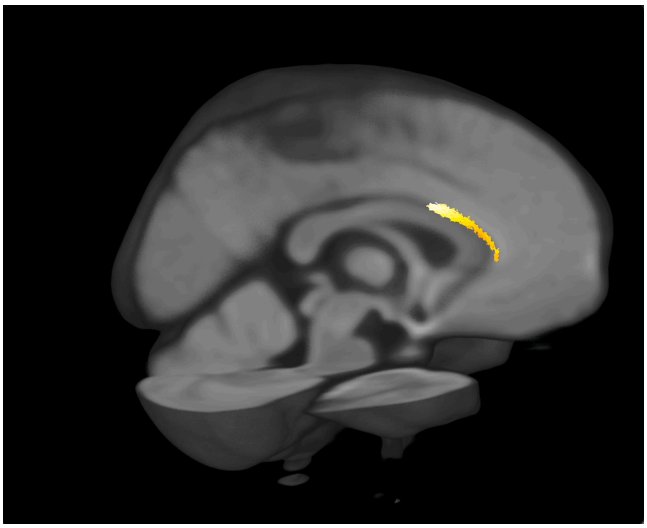


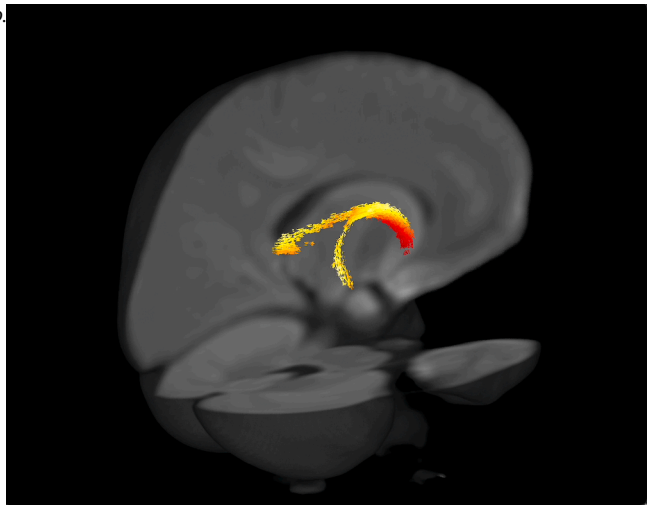
Fig. 2. a. Fixels indicating significant differences in FC–EXT (residual externalizing symptoms) associations between EIG & NIG, within the cingulum, in population-specific template space. b. Post-hoc visualization of group differences in associations between residual externalizing and average FC of significant fixels: NIG show a negative association between cingulum FC and EXT, such that elevated externalizing symptoms are associated with decreased fiber macrostructure. c. Fixels indicating significant differences in FC–EXT associations between EIG & NIG, within the fornix, in population-specific template space. d. Post-hoc visualization of group differences in associations between residual externalizing and average FC of significant fixels: NIG show a positive association between fornix FC and EXT, such that elevated externalizing symptoms are associated with increased fiber macrostructure.



Video 2. A video clip is available online. Supplementary material related to this article can be found online at doi:10.1016/j.dcn.2024.101440.

Differential brain–behavior associations with residual externalizing behaviors were also present within the fornix; participants growing up in family homes displayed positive brain–behavior associations, such that elevated externalizing symptoms associated with increased fornix cross-section, an association that was not exhibited by previously institutionalized adolescents. The fornix is a WM tract connecting the hippocampus and implicated in fear conditioning (Phillips and LeDoux, 1995). A recent FBA study found that, during late childhood and early adolescence, fornix FD was associated with conduct problems (Burley et al., 2021). Given that early life stress, including threat and deprivation, alters fornix microstructure (Choi et al., 2009; Eluvathingal et al., 2006; Yu et al., 2017), it may be that its influence extends to such patterns of associations between WM development and externalizing symptoms. Finally, significant externalizing factor findings were present specifically with WM macrostructure (FC), which has been previously associated with myelination (Malhotra et al., 2019). This suggests that early life neural disturbances may affect myelin formation, in turn altering developmental trajectories of such brain–behavior relations.

Brain and behavior data used here was collected during mid-adolescence, a time of rapid change in both brain and behavioral development. Stress responses, which are sculpted during early childhood and heavily influenced by early adverse experiences, have the potential to be recalibrated based on an individual's current environment (Sisk and Gee,



Video 3. A video clip is available online. Supplementary material related to this article can be found online at doi:10.1016/j.dcn.2024.101440.

2022). Prior analyses within the BEIP sample have observed effects consistent with this recalibration (Wade et al., 2020), as have others in previously institutionalized samples (Gunnar et al., 2019). However, given that we observe altered brain–behavior associations in individuals with different exposure to institutionalization in early childhood, we interpret this as evidence for the long-term consequences of early life experiences. Future work could consider later periods of adolescence, as recalibration following this observation is still possible.

The current analyses build on prior BEIP studies investigating differences between institutionalization groups. First, Wade et al. (2018) did not find significant group differences in internalizing symptoms. Our results indicate no group differences in the neural correlates of internalizing symptoms, which could explain, at least in part, the lack of increased internalizing symptoms within previously institutionalized adolescents. Second, Sheridan et al. (2022) identified group differences in DTI metrics of specific WM tracts. The current fixel-based region--of-interest analyses also revealed between-group differences of fixel metrics in multiple WM tracts, which mostly overlapped with prior DTI findings, suggesting a large correspondence between the two methods. In regions where adolescents with a history of institutionalization (or with prolonged institutionalization) showed increased diffusivity in prior DTI analyses, current fixel-based analyses indicate decreases in micro- and macro-structure. However, there were some inconsistencies between the findings, and this may be explained by both methodological differences (e.g. masks used for WM tracts), as well as lower sensitivity of DTI in detecting group-wise differences when compared to FBA results, particularly in crossing-fiber regions (Dhollander et al., 2021; Kelley et al., 2021).

A limitation of the current analysis includes the diffusion imaging acquisition parameters, which were not optimized for FBA, such as relatively low b-values ($b = 1000$ s/mm^2). Higher b-values allow for decreased signal-to-noise ratio (Tournier et al., 2013), as well as improved estimates of apparent fiber density (Genc et al., 2020), a measure required for accurate and specific estimates of fixel data, especially in regions of crossing fibers (Raffelt et al., 2012). Nevertheless, there is evidence to suggest that fixel-based approaches using data collected with $b = 1000$ s/mm^2 can successfully resolve multiple fibers at reasonable crossing angles (Tournier et al., 2007), and do outperform tensor-based methods (Wilkins et al., 2015). Further, the psychometric data collection method used included caregiver and teacher reports, without the inclusion of adolescent self-reports. This could bias the psychopathology estimates, especially for internalizing symptoms, which are shown to have lower cross-informant correspondence rates as compared to externalizing symptoms (De Los Reyes et al., 2015), with some suggesting this is due to the underreporting of internalizing problems by caregivers (Caqueo-Urízar et al., 2022). An additional limitation of the current study concerns its design: its cross-sectional approach, a relatively small sample size, and the fact that our main results are interactions, leaves our findings underpowered. Future longitudinal studies could investigate these associations in larger samples and at multiple age groups to determine the developmental trajectories of brain–behavior associations in previously institutionalized and never-institutionalized adolescents, and whether such group differences remain over time.

We examined associations between diffusion characteristics of WM and psychopathology in previously institutionalized adolescents and a control group with no history of institutionalization. Here, we demonstrate the moderating effect of early psychosocial deprivation in early life on the relationship between WM structure and psychopathology, both for general psychopathology and specifically for residual externalizing symptoms. Future studies should investigate the developmental trajectories of brain–behavior associations within this population over time. By investigating differences in these pathways between groups, the mechanistic basis of adverse behavioral outcomes in these populations can be better understood. This could inform the development of novel preventive and therapeutic interventions, for example through identifying targets for therapies that promote myelination, recently shown to influence both WM structure and behavioral outcomes in non-human primates (Aggarwal et al., 2024). By considering group differences in brain–behavior associations when developing such therapies, we can tailor them to individual populations, potentially increasing their ability to mitigate risk and improve outcomes.

CRediT authorship contribution statement

Nathan A. Fox: Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Dana Kanel:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Margaret A. Sheridan:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Katie A. McLaughlin:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Charles A. Nelson:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Charles H. Zeanah:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Daniel S. Pine:** Writing – review & editing, Supervision, Funding acquisition.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Charles Zeanah reports a relationship with Irving Harris Foundation that includes: funding grants. Charles Zeanah reports a relationship with The Lumos Foundation that includes: funding grants. Charles Zeanah reports a relationship with The National Heart, Lung, and Blood Institute, NIMH that includes: funding grants. Charles Zeanah reports a relationship with The Substance Abuse and Mental Health Services Administration that includes: funding grants. If there are other authors, they 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.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2024.101440.

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