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Greater age-related changes in white matter morphometry following early life stress: Associations with internalizing problems in adolescence

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ABSTRACT

Early life stress (ELS) is associated with increased risk for internalizing disorders and variations in gray matter development. It is unclear, however, whether ELS affects normative age-related changes in white matter (WM) morphology, and if such maturational differences are associated with risk for internalizing psychopathology. We conducted comprehensive interviews in a cross-sectional sample of young adolescents (N = 156; 89 F; Ages 9–14) to assess lifetime exposure to stress and objective cumulative ELS severity. We used diffusion-weighted imaging to measure WM fixel-based morphometry and tested the effects of age and ELS on WM fiber density and cross-section (FDC), and associations between WM FDC and internalizing problems. Age was positively associated with FDC in all WM tracts; greater ELS severity was related to stronger age-WM associations in several association tracts connecting the frontal lobes with limbic, parietal, and occipital regions, including bilateral superior and inferior longitudinal and uncinate fasciculi (UF). Among older adolescents with greater ELS severity, a higher UF FDC was associated with fewer internalizing problems. Greater ELS severity predicted more mature WM morphometry in tracts implicated in emotion regulation and cognitive processing. More phenotypically mature UF WM may be adaptive against internalizing psychopathology in adolescents exposed to ELS.

1. Introduction

Early life stress (ELS) is associated with increased risk for a range of psychosocial difficulties in adolescence, particularly internalizing disorders (e.g., anxiety and depression) (LeMoult et al., 2019; Stroud et al., 2019). Research suggests that cognitive and affective processes relevant to internalizing problems are vulnerable to the effects of ELS, and that these difficulties persist into adulthood (Pechtel and Pizzagalli, 2011). Importantly, the neural systems that support cognitive and emotional development have protracted maturation in adolescence (Jalbrzikowski et al., 2017; Luna et al., 2015). It is unclear, however, precisely how ELS affects adolescent brain maturation and whether stress-related atypicalities in neurodevelopment are related to risk for internalizing problems.

In this context, the Stress Acceleration Hypothesis posits that adversity during sensitive periods of development leads to accelerated maturation of brain circuitry involved in emotion regulation (Callaghan and Tottenham, 2016). This formulation is supported in animal models where infant and juvenile rats display adult-like fear and extinction learning following stressful rearing (Callaghan and Richardson, 2011), as well as precocious amygdala activity (Moriceau et al., 2009) and axonal myelination (Ono et al., 2008). Research with humans also supports the theory of adversity-driven accelerated maturation of affective neurobiology. Specifically, adolescents have been found to exhibit accelerated volumetric changes in prefrontal, amygdala, and other subcortical regions following ELS (Tyborowska et al., 2018); further, a systematic review suggested that changes in cortical thickness are accelerated following adverse life experiences (McLaughlin et al., 2019). In addition, more mature (i.e., negative) amygdala-prefrontal functional connectivity has been documented in children and adolescents exposed to maternal deprivation; importantly, this precocious emotion regulatory neural phenotype was adaptive as it was associated with fewer anxiety symptoms (Gee et al., 2013). Researchers have found that previously institutionalized adolescents have stronger and more distributed prefrontal functional connectivity to limbic regions during aversive learning than do their never-institutionalized age-matched peers, and that this stronger connectivity predicts improvements in anxiety symptoms in youth exposed to early adversity (Silvers et al.,

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2016). Similarly, greater amygdala-prefrontal connectivity in response to negative stimuli has been found in adolescents with early adversity who have lower, compared to higher, internalizing symptoms (Herringa et al., 2016).

Although age-related functional and structural variations of gray matter regions have been studied in adolescents exposed to varying forms of ELS, it is unclear whether age associations with white matter (WM) tracts are affected by adverse experiences. Researchers have characterized normative WM maturation in adolescence, measured by increasing fractional anisotropy (FA; a measure of water diffusion directionality) (Simmonds et al., 2014), WM volume (Lenroot et al., 2007), fiber density and cross-section (FDC; Dimond et al., 2020; Genc et al., 2018), and myelin content (Kwon et al., 2020), particularly in tracts connecting frontal, temporal, and limbic regions (see review by Lebel et al., 2019). These WM changes are posited to underlie developmental increases in cognitive and affective processing and emotion regulation abilities (Nagy et al., 2004; Simmonds et al., 2014); however, children and adolescents exposed to ELS have altered WM microstructure. Specifically, young adolescents who have experienced early neglect have lower values of FA in the prefrontal cortex (PFC) and WM tracts connecting the PFC with the temporal lobe (Hanson et al., 2013). Further, adolescents with greater sensitivity to ELS have been found to exhibit higher anxiety symptoms and lower FA in the uncinate fasciculus (UF; Ho et al., 2017), a fronto-limbic WM tract implicated in socio-emotional processing (Von Der Heide et al., 2013). Similarly, young adults with a history of maltreatment have been shown to exhibit lower FA of the UF, a neurophenotype that predicted higher internalizing symptoms after subsequent stressful experiences (Hanson et al., 2015). Although the effect of ELS on age-WM associations has not been examined directly, Gur et al. (2019) found that adolescents who had experienced a greater number of traumatic experiences were more likely to be misclassified as adults based on microstructural properties of their fronto-limbic tracts (e.g., UF and superior longitudinal fasciculus and cingulum bundles). Given that adolescence is a period of protracted WM maturation, particularly in fronto-limbic tracts supporting emotion regulation, and because research suggests these WM pathways are altered following ELS, it is important to characterize the effects of early adversity on age-related differences in WM and examine implications for internalizing psychopathology. Further, age-related variations in non-fronto-limbic pathways (e.g., fronto-parietal tracts) might also be affected by ELS, given that widespread WM development continues into adulthood (Yeatman et al., 2014). Characterizing whole-brain WM pathways as they relate to age in adolescents who have experienced varying levels of ELS might elucidate developmental differences in WM tracts and their related functions.

Here, we tested whether ELS moderates age-related variations in WM morphometry in early through mid-adolescence; further we examined internalizing problems in the context of age-related changes in WM. We utilized the recently developed Fixel-based Analysis (FBA) method that quantifies microscopic fiber density and macroscopic fiber caliber (i.e., cross-section) in fiber populations of each voxel (Raffelt et al., 2017). Given the ability of this approach to handle crossing fibers and resolve microstructural and morphological features of WM tracts compared to tensor-based methods, FBA is recommended for characterizing adolescent brain development and the emergence of pathology (Tamnes et al., 2018). We estimated a combined measure of fiber density and cross-section (FDC; as recommended by Raffelt et al., 2017) in adolescents ages 9–14 years who completed a diffusion-weighted MRI scan, and who were interviewed about their exposure to ELS (e.g., abuse, neglect, domestic violence). Based on prior literature documenting protracted WM maturation during adolescence and evolving research suggesting that the development of emotion regulatory circuits is accelerated following ELS, we hypothesized that (1) FDC of major WM tracts will be positively associated with age and (2) more severe ELS will be linked to a stronger age-WM association in the fronto-limbic UF tract (i.e., a more "mature" neural phenotype following ELS). In other words, we expected that at older ages, participants with higher ELS would show a more "mature" UF phenotype (i.e., higher FDC) than their lower ELS peers. We also hypothesized that (3) older adolescents with higher ELS would be characterized by a negative association between UF FDC and internalizing problems, indicating that the more mature UF phenotype is adaptive against internalizing problems. In contrast, we did not expect to find this UF-internalizing association in younger participants given that age-related increases in UF would not yet be present. We specifically investigated the UF in relation to internalizing problems given that this tract has been implicated in internalizing psychopathology in adolescents following exposure to ELS (Hanson et al., 2015; Ho et al., 2017). Finally, although we expected a stronger age-FDC association in the UF given that it is a fronto-limbic tract and would be consistent with the formulations of the Stress Acceleration Hypothesis, we used an exploratory whole brain approach to test whether other tracts that have been shown to have continued development in adolescence, including those involved in cognitive control (e.g., fronto-parietal bundles like the superior longitudinal fasciculus), also have more pronounced age-FDC associations in higher ELS participants. The ten tracts examined in this study are described in the Methods section.

2. Materials and methods

2.1. Sample

The total sample included 190 adolescents who were recruited for a study assessing the effects of ELS on psychobiological characteristics across the pubertal transition. Exclusion criteria included any contraindications to MRI scanning (e.g., non-removable metal in/on the body, pregnancy, claustrophobia), a history of learning disability, neurological disorder, or any serious cognitive or physical challenges that might interfere with the ability to understand or complete procedures, non-fluency in English, and self-reported onset of menses for females (to ensure that adolescents were in early stages of puberty given the parent study's focus on neurodevelopment throughout puberty). Participants and their parent(s)/legal guardian(s) signed assent and consent forms, respectively, to participate in this study, which was approved by the Stanford University Institutional Review Board. All participants were compensated for their time. Of the total sample, 158 individuals successfully underwent the diffusion-weighted MRI scan, 2 of whom were dropped due to scan quality issues. Based on these criteria, the current sample included 156 adolescents (89 females), ages 9–14 years (M = 11.44, SD = 1.08).

2.2. Measures

2.2.1. Cumulative ELS severity

A modified version of the Traumatic Events Screening Inventory for Children (TESI-C; Ribbe, 1996) was used to assess the impact of 30+ types of stressful life experiences (e.g., abuse, physical and emotional abuse, parental separation, domestic violence). Interviewers asked adolescents to provide details about stressful life events in order to assess their severity and impact. Using a modified version of the UCLA Life Stress Interview coding system (Rudolph et al., 2000), three coders blind to the adolescent's subjective severity ratings then rated the objective severity of each event on a 5-point scale (0 = non-impactful; 4=extremely severe impact). A cumulative ELS severity score was computed by summing the maximum objective severity scores for each type of endorsed stressor.

2.2.2. Internalizing problems

Participants completed the Youth Self-Report (YSR; Achenbach, 1991), a widely used and reliable measure (Ebesutani et al., 2011) of children's and adolescents' emotional and behavioral problems. For this study we analyzed the items related to internalizing disorders, such as depression and anxiety.

2.2.3. Pubertal staging

Pubertal stage was estimated using the self-reported Tanner Staging Questionnaire (Morris and Udry, 1980), which is significantly correlated with physician ratings of puberty-related physical development (Shirtcliff et al., 2009). We averaged the Tanner pubic hair and breast/testes ratings to compute an index of overall pubertal development (Dorn et al., 2006), as done previously in this sample (Chahal et al., 2020a, 2020b).

2.3. Acquisition of diffusion imaging

Diffusion-weighted MRI data were collected using a pulsed-gradient spin-echo sequence applied in 60 directions, with anterior-to-posterior phase encoding. Scan parameters included: echo time = 93.5 ms; repetition time = 8500 ms; voxel size = 0.938 × 0.939 × 2.000 mm; slices = 64; flip angle = 12°; b = 2000mm^2. A small number of participants (N = 19; 12.18 %) were scanned using acquisition of 2.00 mm^3 voxel sizes following a scanner upgrade. To control for any effects of this difference in acquisition parameters, we included a 'scan group' variable as a covariate in all analytic models.

2.4. Processing of diffusion imaging

We used Fixel-based Analysis (FBA) to assess the morphometry of WM tracts, as done previously in this sample (Chahal et al., 2020a, 2020b). Briefly, we applied higher-order diffusion models to fiber populations within each voxel (i.e., fixels) in order to estimate a combined measure of fiber density and cross-section (FDC). We estimated FDC per voxel, rather than separating the metrics of fiber density and cross-section because FDC allows for the measurement of both micro- and macro-structural properties of WM. Further, FDC has been shown to be "more sensitive to certain pathologies and more directly interpretable" than are voxel-averaged quantitative measures (e.g., fractional anisotropy) (page 58, Raffelt et al., 2017). All diffusion-weighted MRI data processing was performed using MRtrix3 (Tournier et al., 2019). Following data denoising, and eddy-current induced distortion and motion correction, we estimated a brain mask for each individual and performed bias field correction to eliminate low-frequency intensity inhomogeneities in the images. We then performed 1) intensity normalization across subjects; 2) estimation of a study-specific WM mask; 3) estimation of the group-average response function; 4) up-sampling of diffusion data and brain mask images; 5) estimation of fiber orientation distribution (FOD) using Constrained Spherical Deconvolution via the group average response function; 6) study-specific FOD template generation; 7) registration of subject FOD images to the FOD template; 8) generation of WM template fixel analysis mask; 9) thresholding of peak fixel image; 10) warping of FOD images to template space; 11) segmentation of FOD images to estimate fixels and their fiber density; 12) reorienting of fixel orientations in order to ensure that the subject and template fixels had angular correspondence; 13) assignment of subject fixel to template fixels; 13) computation of fiber cross-section; and 14) computation of a combined measure of fiber density and cross-section (i.e., FDC). A full description of steps taken to compute FDC is available on the MRtrix website (https://mrtrix.readthedocs.io/en/3.0_rc1/fixel_based_analysis/ss_fibre_density_cross-section.html), along with documentation of commands.

The Johns Hopkins University White-Matter Labels and White-Matter Tractography atlases, available through FSL (Jenkinson et al., 2012), were used to extract per-person estimates of the average FDC in the following major WM tracts that have previously been shown to continue maturing in childhood and adolescence (Dimond et al., 2020; Genc et al., 2018; Lynch et al., 2020): callosal body (CCbod), forceps minor (Fmin), forceps major (Fmaj), and bilateral anterior thalamic radiations (ATR), inferior longitudinal fasciculi (ILF), inferior frontal occipital fasciculi (IFOF), superior longitudinal fasciculi (SLF), cortico-spinal tracts (CST), uncinate fasciculus (UF), cingulum bundles (CING). Additionally, microstructural properties of many of these tracts (e.g., IFOF, UF, Fmin, ATR, and SLF) have been implicated in a broad range of emotional disorders (Jenkins et al., 2016).

2.5. Analysis of ELS, age, white matter, and internalizing problems

We conducted a multivariate analysis of covariance (MANCOVA) to test main and interaction effects of age and ELS cumulative severity on FDC of the ten selected WM tracts. We applied false discovery rate correction (FDR) to correct for multiple comparisons assessing age associations and age by ELS interactions on WM tracts. In addition, in a follow-up set of analyses we tested whether ELS experiences related to threat in particular might explain our findings. We calculated ELS threat severity using the same procedure described above for cumulative ELS severity (Section 2.2.1), but only included events associated with threat (e.g., domestic violence, bullying, physical and/or sexual abuse as in King et al., 2020). We did not assess the specific effects of neglect-related ELS because the endorsement of this form of adversity was low in the current sample (only present in 8 of 156 participants).

As stated in our hypotheses, we examined the potential adaptive role of the UF in reducing ELS-related internalizing symptoms, given that researchers have implicated this tract in internalizing disorders, particularly following ELS (Hanson et al., 2015; Ho et al., 2017). Because we expected a steeper positive slope between age and UF FDC in higher-ELS participants, we also posited that higher UF FDC would be present and represent an adaptive neural signature only in older adolescents with higher ELS. Specifically, we tested whether older adolescents (older than the mean age of 11.44 years) with higher ELS severity had a negative association between UF FDC and internalizing problems. We also tested this interaction of UF and ELS on internalizing problems in younger adolescents (below the mean age of 11.44 years), in whom we did not expect UF to moderate the association between ELS and problems. Sex, pubertal status, and scan group (based on acquisition voxel sizes) were included as covariates in all models.

3. Results

Table 1 presents descriptive statistics, and correlations among age, sex, pubertal status, race, cumulative ELS severity, and internalizing problems. As expected, age was positively correlated with pubertal status ($r = .34$, $p < .01$) and average (global) WM FDC ($r = .35$, $p < .01$). Males (M=.31) had greater global WM FDC than did females (M=.29), $T(122.79) = 4.20$, $p < .0001$. This difference may be due to males (M=11.86 years) being, on average, older than females (M=11.11 years), $t(150.70) = 4.71$, $p < .0001$; this age difference was expected given that males and females were recruited in the parent study to be in early stages of puberty, and puberty-related physical development is evident earlier in females than in males (Marceau et al., 2011). Also as expected, cumulative ELS severity was positively associated with internalizing problems ($r = .33$, $p < .01$); males and females did not differ significantly in internalizing problems ($p > .05$).

3.1. Associations of age with white matter fiber density and cross-section

The MANCOVA yielded positive associations between age and FDC in the WM tracts, $F(10,149) = 3.20$ ($p = .001$ for the full model and all tracts had FDR-corrected $ps < .001$; Fig. 1, Table 2). However, as we describe below in Section 3.2, the presence of significant interactions of ELS and age on 6 WM tracts indicates that the main effect of age cannot be interpreted alone in those tracts. The main effect of ELS and pubertal stage on WM tracts were not significant.

3.2. Effects of ELS on associations between age and white matter fiber density and cross-section

Separate ANCOVA models revealed that the interaction of ELS and

Table 1
Participant characteristics.

	Mean (SD)	7	6	5	4	3	2
1. Age (Years)	11.44 (1.08)	$r = .34$*	r=-.01	r=-.02	$F = 0.29$	$r = .34$*	$T = 4.71$* (M > F)
2. Sex (% Female)	57.05 %	$T = 4.20$* (M > F)	T=-1.08	$T = 0.07$	$X^2 = 1.97$	T=-1.73	
3. Pubertal Stage (Tanner Stage)	1.99 (0.72)	$r = .11$	$r = .15$	$r = .08$	F=1.35		
4. Race (% Non-White)	53.85 %	$F = 0.39$	$F = 0.90$	F=2.11			
5. Cumulative ELS Severity	6.70 (5.30)	r=-.05	$r = .33$*				
6. Internalizing Problems	12.27 (9.26)	r=-.08					
7. Average WM FDC	0.30 (0.03)						

Note: *$p < .05$. ELS=early life stress cumulative severity; FDC=fiber density and cross-section.

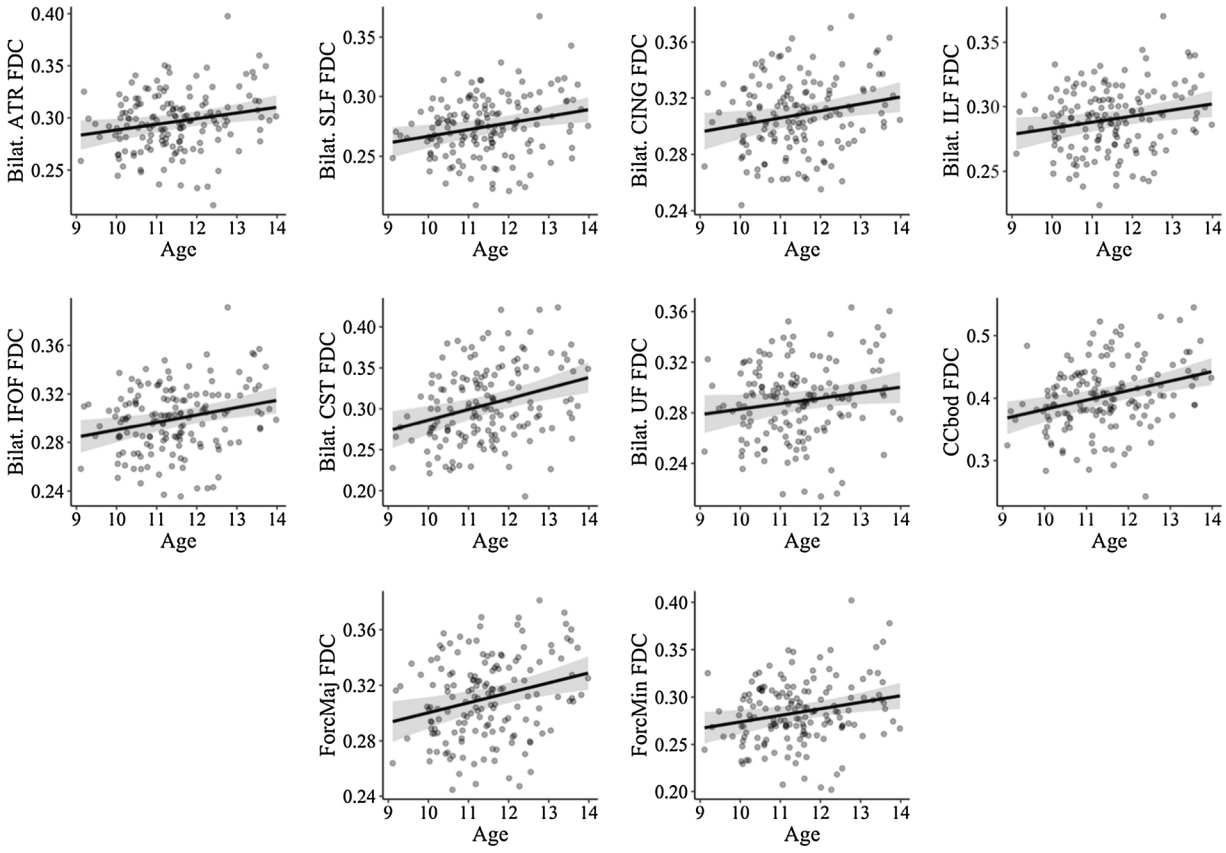

Fig. 1. Age is positively associated with fiber density and cross-section of major white matter tracts.
Note. FDC = fiber density and cross-section; SLF = superior longitudinal fasciculi; ILF = inferior longitudinal fasciculi; IFOF = inferior fronto-occipital fasciculi; CST = corticospinal tracts; Fmin = forceps minor; Fmaj = forceps major; CCbod = callosal body; UF = uncinate fasciculi; CING = cingulum bundles; ATR = anterior thalamic radiations.

Table 2
Associations between age, ELS, and white matter.

WM Tract	Main Effect of Sex			Main Effect of Age			Main Effect of ELS			Age X ELS			Age X ELS
	SS	*F*	*p*	*SS*	*F*	*p*	*SS*	*F*	*p*	*SS*	*F*	*p*	FDR adjusted *p*
ATR	9.06	10.75	.001	12.90	15.26	<.001*	0.47	0.56	.456	4.63	5.50	.020	.039*
SLF	8.54	10.95	.001	14.00	17.94	<.001*	0.05	0.06	.804	4.93	6.32	.010	.034*
CING	14.17	17.00	<.001	12.37	14.84	<.001*	0.45	0.54	.466	2.47	2.96	.087	.097
ILF	17.14	21.92	<.001	14.85	19.00	<.001*	0.49	0.63	.428	4.89	6.25	.013	.034*
IFOF	12.82	16.22	<.001	17.00	21.51	<.001*	0.41	0.52	.472	4.97	6.28	.013	.034*
CST	0.35	0.45	.503	13.33	17.02	<.001*	0.26	0.33	.567	2.36	3.02	.084	.097
UF	6.00	6.80	.010	8.01	9.09	.003*	1.14	1.29	.257	6.29	7.14	.008	.034*
CCbod	1.21	1.36	.246	16.92	18.93	<.001*	0.10	0.11	.744	2.41	2.49	.103	.103
ForcMaj	13.20	16.53	<.001	18.83	23.59	<.001*	0.33	0.41	.523	3.20	3.78	.054	.077
ForcMin	2.08	2.27	.134	10.61	11.58	<.001*	0.11	0.12	.726	4.81	5.43	.023	.039*

Note: *$p < .05$ following FDR correction. ELS=early life stress cumulative severity; FDC=fiber density and cross-section; SLF=superior longitudinal fasciculi; ILF=inferior longitudinal fasciculi; IFOF=inferior fronto-occipital fasciculi; CST=corticospinal tracts; ForcMin=forceps minor; ForcMaj=forceps major; CCbod=callosal body; UF=uncinate fasciculi; CING=cingulum bundles; ATR=anterior thalamic radiations. Scanner acquisition group and pubertal stage were included as covariates.

age was significant for the following WM tracts after FDR correction: bilateral ATR, IFOF, ILF, SLF, and UF, *Fs*(6,149)>5.43, *ps*<.04 FDR corrected (Table 2; Fig. 2). Simple slopes analyses revealed that participants with higher ELS severity (mean +1 SD) had stronger age-FDC associations in these tracts; however, there were not significant associations between age and FDC in participants with average and lower (-1 SD) values of ELS severity (Table 3). We note, however, that when pubertal stage was not included as a covariate in the models, participants with average values of ELS severity also showed positive associations between age and FDC of these six tracts; however, the beta values of the slopes were about twice as large in higher-ELS participants (Tables S1-S2; Fig. S2).

We conducted separate ANCOVAs to test whether the severity of threat-related ELS experiences (e.g., physical and/or sexual abuse, bullying, domestic violence) in particular might be driving our findings. Of the six tracts identified above (i.e., ATR, IFOF, ILF, SLF, and UF), we found significant interactions between ELS threat severity and age in four: bilateral ATR, SLF, IFOF, and UF. As was the case in the above analyses including ELS cumulative severity effects, participants with higher ELS threat severity had more pronounced age associations with the tracts than did participants with lower ELS threat severity (Tables S3-S4; Fig. S3). Of note, however, the association between ELS cumulative severity and ELS threat severity was high (r = .80, p < .001); thus, we could not directly separate the effects of overall ELS severity on age-WM associations from the effects of threat-specific ELS.

3.3. Associations among ELS, age, white matter, and internalizing problems

Younger participants (below the average age of 11.44 years) had a positive association between ELS severity and internalizing problems (*B* = 0.45, *T*(4, 77) = 3.49, *p* < .001); in contrast, there was no association between ELS severity and internalizing problems in older adolescents (above the average age of 11.44 years) (*B* = 0.18, *T*(4, 67) = 1.63, *p* = .108) (Fig. 3).

Further, we found that in older adolescents, there was a significant interaction of UF FDC and ELS severity on internalizing problems, *B*=-0.32, *T*(7, 64)=-3.00, *p* = .004 (Table 4). Simple slopes analyses

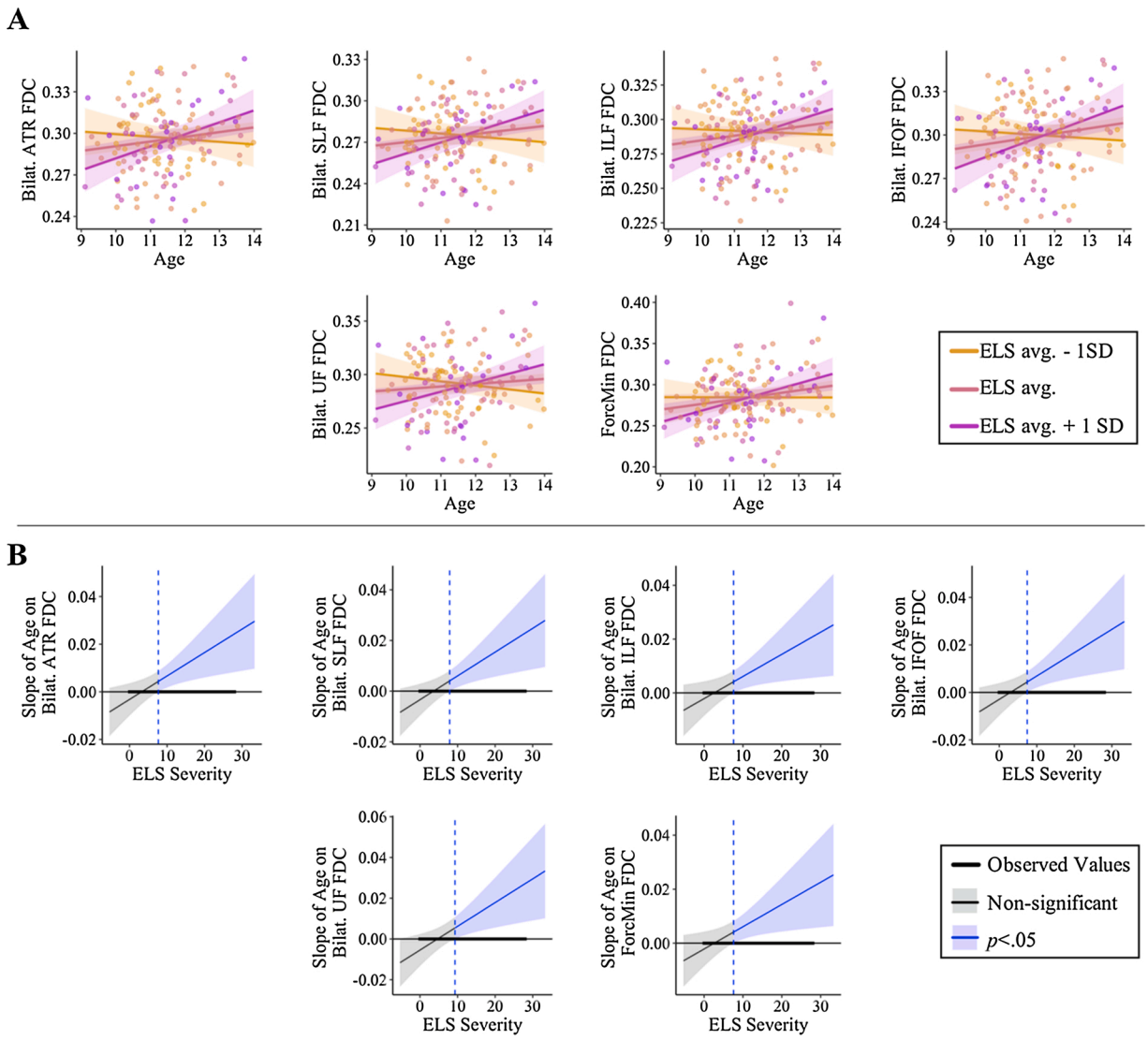

Fig. 2. Age associations with white matter are more pronounced following higher ELS severity.
Note. **A)** Simple slopes of age on white matter fiber density and cross-section (FDC) at different levels of ELS severity. ELS is grouped as -1 SD, average, and +1 SD values only for visualization purposes. These simple slopes are described in Table 3. **B)** Johnson-Neyman plots showing continuous values of ELS severity where the slope of age on FDC was significant vs. not, and the magnitude of slopes. FDC = fiber density and cross-section; ILF = inferior longitudinal fasciculi; IFOF = inferior fronto-occipital fasciculi; Forcmin = forceps minor; UF = uncinate fasciculi; ATR = anterior thalamic radiations; SLF = superior longitudinal fasciculi. Only tracts that exhibited significant age by ELS interactions following FDR correction are displayed.

Table 3
Simple slopes analyses of age associations with white matter tracts by levels of ELS severity.

WM Tract	ELS Avg.−1 SD			ELS Avg.			ELS Avg. + 1SD		
	B	*t*	*p*	*B*	*t*	*p*	*B*	*t*	*p*
ATR	−0.07	−0.61	.544	0.12	1.54	.125	0.32	3.00	.003*
SLF	−0.08	−0.74	.463	0.11	1.44	.152	0.31	2.98	.003*
ILF	−0.04	−0.35	.728	0.13	1.62	.106	0.30	2.83	.005*
IFOF	−0.06	−0.51	.611	0.13	1.65	.100	0.33	3.07	.003*
UF	−0.13	−1.08	.281	0.08	.925	.356	0.30	2.55	.012*
ForcMin	−0.01	−0.02	.986	0.19	2.05	.042*	0.37	3.14	.002*

Note: *$p < .05$; WM=white matter; ELS=early life stress cumulative severity; FDC=fiber density and cross-section; ATR=anterior thalamic radiations; SLF=superior longitudinal fasciculi; ILF=inferior longitudinal fasciculi; IFOF=inferior fronto-occipital fasciculi; UF=uncinate fasciculi; ForcMin=forceps minor; Standardized beta estimates of slopes of age on WM tract fiber density and cross-section at varying levels of ELS severity are reported.

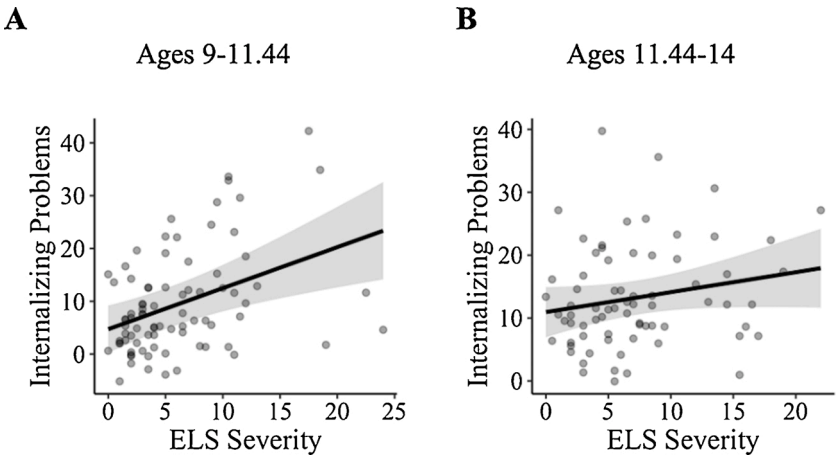

Fig. 3. (A) Early life stress (ELS) cumulative severity is positively associated with internalizing problems only in participants between the ages of 9-11.44 (mean of the sample), (B) though not in those who were older (ages 11.44-14).

Table 4
Main effects and interactions of ELS and uncinate fasciculi FDC on internalizing problems in older adolescents (ages 11.44-14).

	B	*T*	*p*
Age	0.36	−2.00	.051
ELS	0.22	2.06	.044*
Sex	−0.09	−0.42	.679
Pubertal Stage	−0.07	−0.58	.567
UF	−0.11	−1.00	.321
ELS x UF	−0.36	−3.00	.004*
UF Simple Slopes:			
ELS (-1 SD)	0.16	1.06	.294
ELS (Avg.)	−0.13	−1.24	.219
ELS (+1 SD)	−0.43	−3.13	.003*

Note: *$p < .05$;ELS=early life stress cumulative severity score; UF=bilateral uncinate fasciculi fiber density and cross-section. Scanner acquisition group was included as a covariate. Standardized beta estimates of slopes of UF on internalizing problems at varying levels of ELS severity are reported.

Table 5
Main effects and interactions of ELS and uncinate fasciculi FDC on internalizing problems in younger adolescents (ages 9-11.44).

	B	*T*	*p*
Age	−0.07	−0.27	.787
ELS	0.49	3.67	<.001*
Sex	0.41	1.49	.141
Pubertal Stage	0.15	1.17	.247
UF	0.08	0.65	.516
ELS x UF	0.19	1.50	.138

Note: *$p < .05$; ELS=early life stress cumulative severity score; UF=bilateral uncinate fasciculi fiber density and cross-section. Scanner acquisition group was included as a covariate.

revealed that older participants with higher ELS (+1 SD) had a negative association between UF FDC and internalizing problems (B=-0.43, T=-3.13, $p = .002$); in contrast, there was no association between UF and internalizing problems in older participants who had average or lower levels of ELS severity (ps>.05; Table 4). Finally, there were not significant associations between UF FDC and internalizing problems in younger participants (Table 5; Fig. 4).

4. Discussion

In this study we investigated whether age-related differences in WM morphometry, as assessed with fiber density and cross-section (FDC), during adolescence are affected by the cumulative severity of ELS, and whether such neurodevelopmental properties are associated with internalizing problems. Our results suggest that there are stronger positive associations between age and FDC in a number of association tracts following exposure to more severe ELS. Further, our findings suggest that by adolescence (11.44–14 years), higher ELS participants with a more "mature" neural phenotype in the uncinate fasciculi show lower levels of internalizing problems. While the Stress Acceleration Hypothesis (Callaghan and Tottenham, 2016) posits that early adversity is related to more mature fronto-limbic circuitry, we found that a broad range of WM tracts connecting frontal regions with other cortical and subcortical regions had more pronounced age-related associations in adolescents with higher ELS. Given the cross-sectional nature of our study, however, we were not able to determine whether the observed patterns are attributable to accelerated maturation or to between-group differences that might remain stable across adolescence. Future studies

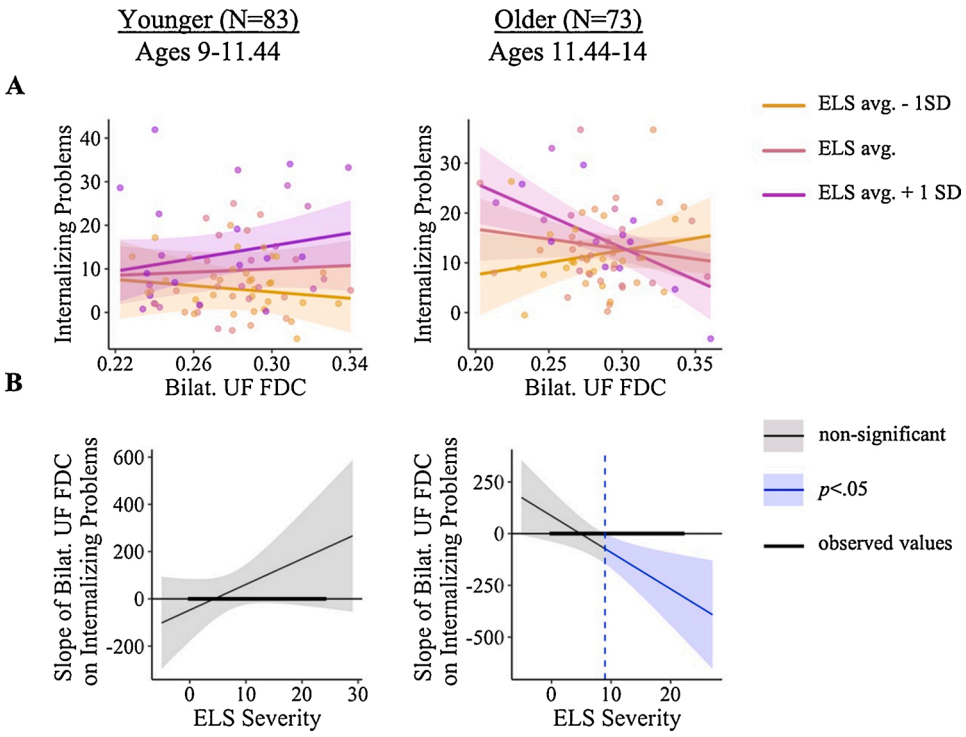

Fig. 4. In older adolescents with higher ELS severity, higher FDC of the UF is associated with lower internalizing problems. (A) Simple slopes analyses showing ELS severity values grouped only for visualization where UF FDC is related to internalizing problems (B) Johnson-Neyman plots showing continuous ELS severity values where the slope of UF FDC on internalizing problems is significant. Older adolescents with higher ELS severity (mean +1 SD) showed a negative association between UF FDC and internalizing problems, though younger adolescents with higher ELS did not show an association between UF FDC and internalizing problems.

using wider age ranges or longitudinal designs should investigate whether lower-ELS participants "catch up" in WM development later in adolescence, or whether these group differences remain throughout development.

4.1. White matter FDC is positively associated with age in in adolescence

Our results are consistent with previous findings indicating that WM morphometry continues to develop in adolescence (Lebel et al., 2019; Simmonds et al., 2014). Although FDC measures are relatively novel, recent work shows that these properties increase throughout childhood (Dimond et al., 2020) and, in particular, from late childhood through early adolescence (Genc et al., 2018). In 9- to 13-year-old youth with two time-points of data, Genc et al. (2018) found that whereas fiber density increases were specific to commissural and association fibers, fiber cross-section increases were widespread. We did not find evidence of tract-specific age associations, likely due to our use of a combined FDC measure, as recommended by Raffelt et al. (2017). Extant research also provides evidence of continued WM maturation throughout adolescence in the forms of increasing fractional anisotropy (e.g., Simmonds et al., 2014), WM volume (Lenroot et al., 2007), and cortical myelin content (Kwon et al., 2020). While previous studies have reported associations between pubertal development and WM microstructural properties (Chahal et al., 2018; Ho et al., 2020; Ladouceur et al., 2012), we did not find significant associations between pubertal staging and WM FDC. This discrepancy may be due to our relatively homogeneous sample in terms of pubertal staging; the majority of participants (80.77 %) were Tanner Stage 2.5 or below as a result of the parent study design. Another difference between this study and prior research is that we examined combined micro- and macrostructural measures of WM fibers at the voxel level (i.e., fixel), whereas previous work examined only microstructural diffusion properties (e.g., fractional anisotropy).

4.2. Fronto-limbic WM associations with age are amplified following more severe ELS

As hypothesized, the positive association between age and FDC of the UF was stronger in adolescents with higher severity of ELS. However, we also found that following severe ELS, there was a more mature phenotype, characterized by higher FDC, in tracts connecting frontal regions with occipital (IFOF and ILF), thalamic (ATR), posterior parietal (SLF), and other frontal (Fmin) regions (Webb, 2017). The ILF, IFOF, and sub-components of the SLF are association fiber tracts that have been found to support visual attention and somatosensory processing; in contrast, the UF is posited to support cognitive-emotion interactions and the ATR has been implicated in reward-related attention and affect regulation (Coenen et al., 2012; Schmahmann and Pandya, 2009; Wright et al., 2015). Although the posited roles of these tracts vary, they are all implicated in affective functioning. Indeed, a transdiagnostic meta-analysis showed that emotional disorders (e.g., depression, anxiety, posttraumatic stress disorder) are characterized by shared abnormalities in microstructural properties of the IFOF, UF, forceps minor, ATR, and SLF (Jenkins et al., 2016). Attentional and cognitive capacities related to emotion processing are supported by these tracts. For example, the ILF and IFOF have been shown to be integral in facial emotion processing (Philippi et al., 2009), and fractional anisotropy of the SLF has been shown to be positively correlated with executive functions (Urger et al., 2014). Together, the tracts identified in this study (i.e., those showing stronger age associations following ELS) connect prefrontal, visual, and affective regions that are critical in cognitive and socioemotional processing (Bachevalier and Loveland, 2006). While the Stress Acceleration Hypothesis is focused on fronto-limbic circuitry in particular, we show here that WM tracts connecting the frontal lobes with other regions involved in cognitive and affective processing appear to have a more "mature" phenotype in youth exposed to adverse life events.

Although it may seem that only in participants with higher levels of ELS were there positive associations between age and FDC of the above-mentioned tracts, when we removed the pubertal stage model covariate, even participants with average levels of ELS showed age-FDC relations.

However, an important difference is that the estimated effect of age on FDC was twice the magnitude for higher-ELS participants compared to those with average levels of ELS exposure. Given that there was not an association between age and FDC in lower-ELS participants, there may be a graded effect of ELS severity on the rate of development of specific WM tracts. As we noted previously, however, the cross-sectional nature of the study and limited age range (9–14 years) of the sample does not allow us to make claims about accelerated maturation. A sample with a wider age range, ideally assessed longitudinally, is needed to determine whether the findings we observe are attributable to stable group differences across the period of WM development into adulthood or if they reflect developmental shifts consistent with accelerated maturation (e.g., lower-ELS youth eventually "catch up" at later ages).

4.3. Greater FDC in fronto-limbic tracts is associated with lower internalizing problems in older adolescents exposed to greater ELS

As theorists have posited in the context of atypical development of gray matter, adult-like WM properties, particularly in fronto-limbic circuitry, following adverse life events may represent adaptations that attempt to match neurobiology with an unstable and stressful early environment (Belsky, 2019; Callaghan and Tottenham, 2016). In older participants (ages 11.44–14 years) with higher ELS severity, a more mature uncinate phenotype (i.e., higher FDC) was related to fewer internalizing problems, although this was not the case for younger participants (ages 9–11.44 years) with higher ELS. These findings are also consistent with previous findings of lower anxiety symptoms in youth with more mature (i.e., negative) amygdala-medial PFC functional connectivity following severe neglect (Gee et al., 2013), and of lower internalizing symptoms in adolescents with childhood adversity who exhibit enhanced amygdala-prefrontal connectivity to negative stimuli (Herringa et al., 2016). The UF is recognized as the main WM pathway connecting the amygdala with the PFC (Wakana et al., 2004), and greater WM connectivity between these regions has been shown to be associated with attenuated amygdala reactivity (Goetschius et al., 2019). Indeed, lower FA in the UF has been documented in adolescents with depression (LeWinn et al., 2014) and anxiety (Hanson et al., 2015; Ho et al., 2017), suggesting that this tract underlies effective emotion regulation. Our findings are consistent with previous work indicating that exposure to ELS is associated with more mature fronto-limbic circuitry, and we extend this work by showing that associations of age with the morphometry of WM tracts involved in cognitive and affective processing are more pronounced in adolescents with more severe experiences of ELS. Further, we found that higher UF FDC (i.e., a more "mature" neurophenotype) in older adolescents with higher ELS severity might be adaptive and related to lower internalizing problems

It is noteworthy that there were not significant associations among ELS, UF FDC, age, and internalizing problems in younger adolescents. This may be due to the finding that fronto-limbic FDC was significantly differentiated by ELS at older, but not at younger, ages (see Fig. 2). It is possible that these tracts diverged following accelerated maturation in adolescents with higher ELS, and that significant ELS-related differences in fronto-limbic FDC were observable only in later adolescence; however, this is speculative given our cross-sectional sample. At younger ages, we did not find ELS-related differences in fronto-limbic FDC; thus, we did not detect an effect of FDC on internalizing problems. Future work with longitudinal samples would be able to examine when in development WM divergence begins following ELS and how these neurodevelopmental trajectories are related to changes in internalizing symptoms.

It is important to note that while the more mature UF phenotype was related to lower internalizing problems in older participants, it is possible that more "mature" morphology of fronto-limbic WM is not adaptive in the long term. Specifically, Callaghan and Tottenham (2016) argue that accelerated development of limbic brain regions may be followed by decreased plasticity in adulthood and greater risk for fear-related psychopathology, as has been documented in rodents with decreased prefrontal-amygdala plasticity (Callaghan and Tottenham, 2016; Fragale et al., 2016). Speeded maturation of the emotion system may also come at the cost of delayed development in other systems (e.g., reward and cognitive) (Herzberg and Gunnar, 2020). Longitudinal studies examining WM pathways involved in reward, emotion, and cognitive processing are necessary to understand whether ELS differentially affects age-related variations in these neural systems and if heterochronous trajectories are accompanied by windows of precocious plasticity and increased risk for psychopathology.

4.4. Limitations

We should note three limitations of the present study. First, we did not examine *longitudinal changes* in WM and, therefore, cannot test the Stress Acceleration Hypothesis directly. Rather, we examined *age-related variations* in WM as they relate to ELS severity. Future work should seek to test more directly and explicitly whether adverse experiences are followed by steeper increases in FDC of fronto-limbic WM tracts, and whether neurodevelopmental trajectories are accompanied by variations in levels of internalizing problems. Second, we did not examine sex differences in age-WM associations following varying levels of ELS severity, given that this was not a primary aim of the study. To ensure that all participants were in early puberty at entry into this study, males in the sample were slightly older than females, and average FDC values were also higher in males. Given these complexities and because males and females did not differ in internalizing problems, we did not probe sex differences in age-ELS associations with WM and internalizing problems. Finally, we used a cumulative risk approach rather than a dimensional or adversity-specific approach to examine how varying levels of ELS severity might affect age associations with WM tracts in a community sample of adolescents. While we think that it is important to consider the impact of different types of ELS (e.g., neglect and threat) on neurophenotypes, including WM, from a dimensional perspective (McLaughlin et al., 2020), very few participants in our sample endorsed experiences of neglect. In contrast, threat-related ELS exposure was more common in our sample, and co-exposure to different types of ELS exposure was high (King et al., 2020). Although we did not have sufficient levels of neglect endorsement in our study to separate the effects of neglect from those of threat, we showed in our supplemental follow-up analyses that in four of the six tracts in which there was an interaction of age and ELS cumulative severity, there were also interactions of age and ELS threat severity. We should note that because the severity of threat-specific ELS in our sample was strongly correlated with overall ELS severity, we could not determine whether general ELS or threat in particular affected age-WM associations. Future studies with larger samples experiencing a range of early adverse experiences should test whether age associations in WM tracts are evident in adolescents who experienced ELS in general, or are more pronounced in those who experienced specific types of adversity.

5. Conclusion

In a community sample of adolescents, we tested whether cumulative severity of ELS affects age-related variation in WM morphometry and internalizing problems. Across all examined WM tracts, FDC was positively associated with age; ELS severity moderated this association, such that youth with higher ELS severity had stronger positive associations between age and several association WM tracts connecting the frontal regions with occipital, temporal, limbic, and parietal regions. Further, a more mature UF WM phenotype was related to lower levels of internalizing problems in older adolescents with higher ELS severity. Cognitive and affective WM circuitry may develop earlier or at a faster rate as an adaptation to the environment in adolescents who are exposed to a greater severity of stressful experiences. Longitudinal research is needed to characterize trajectories of WM development following

varying levels and dimensions of exposure to ELS in order to determine whether ELS-related variations in WM remain over the course of development or whether these differences are attenuated with age.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100899.

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