Disentangling the Effects of Early Caregiving Experience and Heritable Factors on Brain White Matter Development in Rhesus Monkeys

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Abstract

Early social experiences, particularly maternal care, shape behavioral and physiological development in primates. Thus, it is not surprising that adverse caregiving, such as child maltreatment leads to a vast array of poor developmental outcomes, including increased risk for psychopathology across the lifespan. Studies of the underlying neurobiology of this risk have identified structural and functional alterations in cortico-limbic brain circuits that seem particularly sensitive to these early adverse experiences and are associated with anxiety and affective disorders. However, it is not understood how these neurobiological alterations unfold during development as it is very difficult to study these early phases in humans, where the effects of maltreatment experience cannot be disentangled from heritable traits. The current study examined the specific effects of experience ("nurture") versus heritable factors ("nature") on the development of brain white matter (WM) tracts with putative roles in socioemotional behavior in primates from birth through the juvenile period. For this we used a randomized crossfostering experimental design in a naturalistic rhesus monkey model of infant maltreatment, where infant monkeys were randomly assigned at birth to either a mother with a history of maltreating her infants, or a competent mother. Using a longitudinal diffusion tensor imaging (DTI) atlas-based tract-profile approach we identified widespread, but also specific, maturational changes on major brain tracts, as well as alterations in a measure of WM integrity (fractional anisotropy, FA) in the middle longitudinal fasciculus (MdLF) and the inferior longitudinal fasciculus (ILF), of maltreated animals, suggesting decreased structural integrity in these tracts due to early adverse experience. Exploratory voxelwise analyses confirmed the tract-based approach, finding additional effects of early adversity, biological mother, social dominance rank, and sex in other WM tracts. These results suggest tract-specific effects of postnatal maternal care experience versus heritable or

biological factors on primate WM microstructural development. Further studies are needed to determine the specific behavioral outcomes and biological mechanisms associated with these alterations in WM integrity.

Keywords

Diffusion tensor Imaging; maternal care; infant maltreatment; nonhuman primate; uncinate fasciculus; inferior longitudinal fasciculus; middle longitudinal fasciculus; temporal white matter

Introduction

Early social experiences, particularly maternal care, shape behavioral and physiological development (Curley and Champagne, 2016; Drury et al., 2017; Howell et al., 2016; Sánchez et al., 2001). Thus, it is not surprising that adverse caregiving, a form of early life stress (ELS), is a major risk factor for psychopathology, including anxiety, depression, substance abuse, and behavioral disorders across the lifespan (Carr et al., 2013; Danese and Tan, 2014; Gunnar and Quevedo, 2007; Pechtel and Pizzagalli, 2011; Shonkoff et al., 2012; Shonkoff and Bales, 2011; Teicher et al., 2003). One particularly devastating and widespread form of early life adversity is infant maltreatment. In 2016 an estimated 676,000 children were affected in the US alone, with 68% of victims being younger than 5 years of age, with those in the first year of life experiencing the highest rates of abuse and neglect (Children's Bureau, 2018). In addition to the human toll, in 2008 the lifetime economic cost of new cases of child maltreatment in the US has been estimated to be $428 billion (Peterson et al., 2018). Given these staggering human, health, and economic consequences, it is of vital importance to understand the neurobiological mechanisms that underlie the adverse behavioral and psychological outcomes associated with child maltreatment in order to identify tractable neurodevelopmental targets for prevention and treatment.

One potential neurobiological mechanism involves the impact of ELS on the development of brain structural connectivity, including brain white matter (WM) (De Bellis et al., 1999; Hanson et al., 2013; Brittany R. Howell et al., 2013; McCrory et al., 2012; Ohashi et al., 2017; Teicher et al., 2003). Brain WM undergoes massive developmental changes during early life, including increases in volume due to myelination, dendritic pruning, etc. making these developmental processes vulnerable to environmental factors during infancy and childhood (Deoni et al., 2012; Dubois et al., 2014; Geng et al., 2012). Indeed, there is also evidence that myelination and other developmental processes are sensitive to stress and glucocorticoids (Brittany R. Howell et al., 2013; Jauregui-Huerta et al., 2010; Liston and Gan, 2011), suggesting that elevated levels of stress hormones related to infant maltreatment and other ELS experiences could affect the development of brain WM microstructural integrity during infancy and childhood.

Microstructural integrity of WM bundles can be assessed *in vivo* and therefore longitudinally using diffusion tensor imaging (DTI), providing a powerful tool to study neurodevelopmental changes in brain WM tracts (Le Bihan, 2003). DTI allows quantification of water diffusion on a microscopic scale using a variation of a typical MRI magnetization sequence (Jones and Leemans, 2011). Diffusion in the brain is informative

because myelinated axons restrict what would otherwise be non-directional diffusion (i.e. isotropic) of water, resulting in anisotropy (Le Bihan et al., 2001). This directional diffusion can be quantified by fractional anisotropy (FA), which is the ratio of diffusion parallel to the fibers (i.e. axial diffusivity, AD) to diffusion perpendicular to the fibers (i.e. radial diffusivity, RD). Thus, FA can be affected by either changes in diffusion perpendicular to the tract, which decreases with increased axonal myelination (Zhang et al., 2009), or to changes in diffusion parallel to the tract, which increases with axonal density, caliber, and microtubular packing and organization (Kumar et al., 2012). Thus, higher FA values can be interpreted as increased WM tract integrity due to increased myelin or increased fiber tract organization. FA was the main diffusion property selected for this study (although AD, RD and mean diffusivity - MD, the mean diffusion across and parallel to the fibers – are also presented) because it increases across early development (Cohen et al., 2016; Deoni et al., 2012; Shi et al., 2013), it has been associated with variations in behavior, and is sensitive to early caregiving experience (Fields, 2008; B.R. Howell et al., 2013; Scholz et al., 2009).

Cortico-limbic and temporal circuits (including WM bundles such as the uncinate fasciculus -UF-, the inferior longitudinal fasciculus -ILF-, middle longitudinal fasciculus -MdLF-, and fornix) appear to be particularly sensitive to ELS. These circuits are key for processing of social stimuli (e.g. visual, auditory) and emotional regulation (Dannlowski et al., 2012). Early adversity has been previously related to WM microstructural alterations in these circuits in individuals with histories of adverse caregiving, including institutional rearing and childhood maltreatment (Bick et al., 2015; Dannlowski et al., 2012; De Bellis et al., 1999; Eluvathingal et al., 2006; Govindan et al., 2010; Hackman and Farah, 2009; Hanson et al., 2013; Kumar et al., 2014; McCrory et al., 2012; Teicher et al., 2003, 2014). These regions are also sensitive to ELS in animal models (Bolton et al., 2018; Coplan et al., 2016; Brittany R. Howell et al., 2013; Howell et al., 2017, 2016, 2014; McEwen, 2008). Additionally, alterations in these WM regions are implicated in the psychopathologies and several of the affective disorders for which ELS is a risk factor (Dannlowski et al., 2012; Fields, 2008; Pechtel and Pizzagalli, 2011; Thomason and Thompson, 2011). Taken together this evidence suggests that ELS results in alterations in cortico-limbic WM tracts that have been linked with increased risk for psychopathology.

Despite the link between early adverse experiences and WM alterations it is not clear how these alterations unfold during human development, as it is very difficult to study these early phases in humans because the effects of adversity cannot be disentangled from heritable traits (e.g. higher stress and emotional reactivity), or nutritional, medical or socioeconomic factors. There is also evidence that early adversity- and maltreatment-related traits can be transmitted from generation to generation in humans and nonhuman primates, and that genetic and epigenetic mechanisms may be involved (Bowers and Yehuda, 2015; Collishaw et al., 2007; Fairbanks, 1989; Franklin et al., 2010; Huizinga et al., 2006; Kaplow and Widom, 2007; KINNALLY et al., 2013; Kinnally and Capitanio, 2015; Maestripieri, 2005; Moog et al., 2018; Santavirta et al., 2018; Tarullo and Gunnar, 2006; Widom et al., 2015). Thus, the current study examined the specific effect of early caregiving ("nurture") and heritable factors ("nature") on the developmental trajectories of major brain WM tracts in primates from birth through the juvenile period using a randomized cross-fostering experimental design in a naturalistic rhesus monkey model of infant maltreatment.

Nonhuman primate models such as rhesus macaques (*Macaca mulatta*) have a critical translational value for humans when studying the effects of early adverse social experience, particularly on neurodevelopment, for several reasons. Biological and behavioral similarities that make rhesus monkeys ideal for studying neurodevelopment include prolonged gestation of a single offspring, strong social and mother-infant bonds (Hinde and Spencer-Booth, 1967) maturational stage of the brain at birth, and neurodevelopmental patterns (particularly those of WM development in the few published reports, Gibson, 1991; Shi et al., 2013). Rhesus monkeys develop approximately four times faster than humans, making longitudinal experiments designed to assess changes in developmental trajectories such as the current study more feasible. Rhesus monkeys are also more closely related to humans phylogenetically than other model organisms (e.g. rats or mice), and the developmental effects of the early environment in development, particularly maternal care, show strong similarities with those of humans (Hinde and Spencer-Booth, 1967; Howell et al., 2014; Maestripieri, 1999; Sánchez et al., 2001). Rhesus monkeys also exhibit spontaneous infant maltreatment (Maestripieri and Carroll, 1998), an adverse form of caregiving reported in several other primate species (Brent et al., 2002; Johnson et al., 1996; Maestripieri and Carroll, 1998; TROISI and D'AMATO, 1984).

Here we studied the effects of spontaneous infant maltreatment in rhesus monkeys, which occurs in approximately 2–5% of rhesus dams (Howell et al., 2016; Maestripieri and Carroll, 1998; McCormack et al., 2006). We operationalized maltreatment using two types of behavior, physical abuse and maternal rejection (thought to be a form of neglect) (Maestripieri and Carroll, 1998; McCormack et al., 2006), which cause infant distress and elevations in stress hormones (Drury et al., 2017; Brittany R. Howell et al., 2013; Koch et al., 2014; McCormack et al., 2009, 2006). They occur predominantly during the first 3–6 months of life, with many maltreating mothers showing these behaviors as early as the first 2 weeks of life (Maestripieri and Carroll, 1998; McCormack et al., 2006). Maltreatment shows transgenerational transmission along the maternal line (Maestripieri, 1998) in part via experience (i.e. females maltreated as infants are likely to maltreat their own infants), as shown in studies using a cross-fostering design (i.e. Maestripieri, 2005). Previous reports using this NHP model of infant maltreatment have identified negative outcomes in offspring, including increased anxiety and emotional responses, social deficits and alterations in stress neuroendocrine and immune systems throughout infant development and into adolescence (Drury et al., 2017; B.R. Howell et al., 2013; Howell et al., 2017, 2014; Koch et al., 2014; Kohn et al., 2014; Maestripieri, 1998; Maestripieri et al., 2000; McCormack et al., 2009, 2006, Sanchez et al., 2015, 2010, 2007). Our group has also identified neurodevelopmental alterations in amygdala volume and cortico-limbic circuits such as the UF associated with altered emotional reactivity (Howell et al., 2017, 2014). These effects of infant maltreatment in rhesus monkeys are consistent with alterations reported in children that experienced maltreatment and other forms of adverse caregiving as discussed above, which supports the construct validity of this animal model for uncovering the underlying neurodevelopmental mechanisms. Given the evidence that maltreatment can be perpetuated from generation to generation in humans and NHPs, and that genetic and epigenetic mechanisms can result in behavioral traits associated with maltreatment (Bowers and Yehuda, 2015; Collishaw et al., 2007; Fairbanks, 1989; Franklin et al., 2010; Huizinga et al., 2006; KINNALLY et al., 2013;

Kinnally and Capitanio, 2015; Maestripieri, 2005; Moog et al., 2018; Santavirta et al., 2018; Tarullo and Gunnar, 2006; Widom et al., 2015), a critical contribution of our study is to disentangle the role of adverse caregiving experience ("nurture") from that of potential heritable phenotypes ("nature") using a validated animal model and a cross-fostering, randomized, well-controlled design not possible in human studies.

Therefore, the primary goal of this study was to examine the developmental trajectories of primate cortico-limbic and temporal WM tracts sensitive to ELS and with putative roles in socioemotional behavior from birth through the juvenile period while disentangling the specific impact of postnatal adverse experience (infant maltreatment) from heritable factors. We investigated this question using two different strategies: a hypothesis-driven approach focusing on specific WM tracts that are part of cortico-limbic and temporal brain circuits previously shown to be sensitive to ELS (e.g. the UF, ILF, MdLF, the fornix, and the corpus callosum - CC) and a second, data-driven, exploratory voxelwise approach, that examined developmental differences in WM tracts across the entire brain. In addition to the effects of maternal care and heritable factors from the biological mother, we also examined the effects of other important genetic and social factors such as sex and social dominance rank in our statistical models.

Methods

Subjects and Housing

A total of 42 infant rhesus monkeys (*Macaca mulatta*) were studied longitudinally from birth through 18 months of age (early juvenile period) to examine the effects of variations in maternal care on brain WM development as part of a larger longitudinal study that examined other biobehavioral outcomes (Drury et al., 2017; Howell et al., 2017; Mccormack et al., 2015). Of those, 20 infants were raised by dams with competent maternal care (control, C: 9 male, 11 female) and 22 were raised by maltreating dams (maltreating, M: 14 males, 8 females; see Table 1, "Supplemental Material", and the "*Crossfostering*" section below for group breakdown by biological dam based on our random assignment to experimental group at birth). Animals were born and housed at the Yerkes National Primate Research Center (YNPRC) Field Station, Lawrenceville, GA for the entire study. Subjects lived with their mothers and families in large, complex social groups consisting of 75–150 adult females, their sub-adult and juvenile offspring, and 2–3 adult males. This social complexity also enabled us to balance the distribution of social dominance ranks (high, medium and low social status), in addition to sex, across our experimental caregiving groups. Altogether our social experimental setting and design allowed examination of not only the effects of maternal care and biological heritable traits, but also of sex and social dominance rank on neurodevelopmental measures. The groups were housed in outdoor compounds (approximately 100ft x 100ft) with access to a climate controlled indoor housing area. Standard high fiber, low fat monkey chow (Purina Mills Int., Lab Diets, St. Louis, MO) and seasonal fruits and vegetables were provided twice daily, in addition to enrichment items. Water was available *ad libitum.* All the procedures described here were performed in accordance with the Animal Welfare Act and the U.S. Department of Health and Human Services "Guide for the Care and Use of Laboratory Animals", and were approved by the

Emory Institutional Animal Care and Use Committee. Researchers were blind to group assignment whenever possible. Specifically, those collecting behavior were not blind all blind, as the behavioral observations were used to define group assignment, although they were whenever possible. Those that collected and QCed the imaging data, as well as those that built the DTI atlases were blind to group.

Cross-fostering design

All infants were randomly assigned at birth to be reared by a foster dam with either a history of competent maternal care (control) or of infant maltreatment (maltreating) in an effort to disentangle the effects of heritable and biological factors that may interact with the effects of early caregiving experience on WM development. Newborn monkeys were cross-fostered to an unrelated female at birth (except for 6 infants cross-fostered 24 hours, 2 others at 48 hours and 1 at 72 hours after birth), counterbalancing groups by sex, biological mother, social dominance rank, and assigning infants from different matrilines and paternities to ensure high genetic and social diversity, as previously reported (Drury et al., 2017; Howell et al., 2017; Maestripieri, 2005). Infants were removed from their biological dams and introduced to their foster dams within 5 minutes of initial separation, resulting in a high adoption success rate (83%: 35 out of 42 were immediately successful). In the few cases where the foster dam did not immediately accept the foster infant (7 in this study) several strategies were employed to encourage adoption, including keeping dam and foster infant in close proximity in a quiet room, lightly anesthetizing the dam with ketamine (a known amnesic compound) and allowing the foster infant to nurse to increase endogenous maternal oxytocin, or administering exogenous oxytocin. If none of these strategies worked within a couple of hours, infants were returned to their biological mothers and excluded from the study. As shown in Table 1 (Supplemental Materials), of the 20 infants raised by foster control dams, 11 were biological infants of control mothers (CC subjects, as detailed in Table 1 of Supplemental Material: 6 males, 5 females) and 9 were born to maltreating mothers (MC: 3 males, 6 females). Of the 22 infants raised by maltreating dams, 12 were biological infants of control mothers (CM: 9 males, 3 females), and 10 were born to maltreating mothers (MM: 5 males, 5 females).

Behavioral observations: characterization of maternal care

A detailed description of the infant rhesus maltreatment model and methods for behavioral characterization of competent maternal care versus infant maltreatment is provided in previous publications (Drury et al., 2017; Howell et al., 2017; Maestripieri, 1998; McCormack et al., 2009, 2006). Briefly, infant focal observations were performed beginning at birth and continued over the first 3 months of life to characterize early maternal care experience using an adaptation of a well-established rhesus monkey ethogram (Altmann, 1962; McCormack et al., 2006). Thirty-minute-long observations were performed on separate days (5 days/week during month 1 for a total of 20 observations; 2 days/week during month 2 for a total of 8 observations; and 1 day/week during month 3 for a total of 4 observations) for a total of 16 hours per mother-infant pair. Observations were collected between 7 and 11 AM, when animals are most active. This observation protocol is optimal to document infant maltreatment in this species, given that physical abuse is the highest during month 1and stops by month 3 (Drury et al., 2017; Maestripieri, 1998; McCormack et al.,

2006). Competent maternal care was defined as species-typical behaviors such as nursing, cradling, grooming, ventral contact and protection (retrieve from potential danger, restrain) of the infant. In contrast, maltreatment was defined as the comorbid occurrence of physical abuse (operationalized as violent behaviors directed towards the infant that cause pain and distress, including dragging, crushing, throwing) and infant rejection (i.e. prevention of ventral contact and pushing the infant away). We did not observe any instances in which subjects were the receivers of abusive behaviors from anyone other than their own maltreating foster dams. Physical abuse and rejection are highly comorbid in nonhuman primates, similarly to humans (Guzman et al., 2016; Howell et al., 2016) and thus represent a homogenous maltreatment experience. This comorbidity provides face validity for human studies in which physical abuse and neglect also co-occur (Cicchetti and Toth, 1995). Both abuse and rejection cause high levels of infant distress (e.g. scream vocalizations) and elevations in stress hormones (Drury et al., 2017; B.R. Howell et al., 2013; Maestripieri, 1998; McCormack et al., 2006; Sanchez, 2006). Control foster mothers in this study exhibited competent maternal care and did not exhibit physical abuse or rejection (Drury et al., 2017; Howell et al., 2017). Abuse and rejection rates were calculated across the first 3 postnatal months. Inclusion criteria in the maltreated group involved at least 3 instances of observed physical abuse. Other infant behaviors collected included affiliative behaviors (e.g. contact, grooming), anxiety-like behaviors (e.g. yawning, scratching, and body shakes (Maestripieri et al., 1992; Troisi et al., 1991), and general behavior (e.g. eating, drinking, passive).

MRI data acquisition and processing

T1 weighted (T1w), T2 weighted (T2w), and diffusion weighted images (DWI) were acquired during infancy (at 2 weeks, and 3 and 6 months) and the early juvenile period (at 12 and 18 months of age). Twenty-one subjects had usable data for all 5 time points, sixteen had usable data for 4 time points, four had usable data for 3 time points, and one had usable data from 2 time points (see details in Table 1, Supplemental Material). Data were considered usable if they passed the QC procedures described in the next paragraph. The statistical methods applied accommodate missing data (see Statistics section for details). A total of 181 scans were used for this study. Images were acquired on a 3T Siemens Trio scanner (Malvern, PA) at the YNPRC Imaging Center using an 8-channel array, transmit and receive knee volume coil. Animals were separated from their mothers for approximately 4 hours total for scanning. This included 30 min for scan preparation (e.g. anesthesia, intubation, positioning in scanner), 3 hours of active scanning, and 20–30 minutes post anesthesia recovery. The subjects were scanned supine under isoflurane anesthesia (0.8–1% isoflurane, inhalation). A custom-made head holder with ear bars and a mouthpiece was used to secure and prevent movement of the head in order to avoid motion artifacts. A vitamin E capsule was placed on the right temple to identify the right brain hemisphere. Animals were intubated, administered dextrose/NaCl (I.V.) for hydration, and placed on an MRI-compatible heating pad to maintain temperature. Physiological measures (i.e. heart rate, temperature, blood oxygenation) were monitored and maintained throughout the scans following YNPRC veterinary protocols. After the scan and complete recovery from anesthesia, subjects were returned to their mothers, and the mother-infant dyad returned to their social group.

T1w data were acquired for image co-registration with DWI data using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence with the following parameters: TI/TR/TE= 950/3000/3.3 ms; 4 averages; voxel size: 0.6 mm isotropic ($0.2\ mm^3$) resolution. T2w images were collected using a fast-spin echo sequence in the same direction as the T1 (TR/TE=7,900/125ms, voxel size=0.5×0.5×1.0mm – $0.25 mm^3$, 10 averages) to help with anatomical identification of tissue borders, as well as for propagating structural brain masks to the DWI data. DWI images were collected with the following parameters: single-shot dual spin-echo EPI sequence with GRAPPA (R=3), voxel size: 1.3 mm isotropic ($2.19 mm^3$) with zero gap, 60 directions, TR/TE=5000/86 ms, 40 slices, FOV: 83 mm, b: 0, 1000 s/mm², 12 averages. All preprocessing, including eddy current and motion correction as well as automatic removal of artifact rich images, was performed using the DTIPrep software developed by the UNC Neuroimaging Research and Analysis Laboratories (NIRAL) (Oguz et al., 2014). DTIPrep is specifically designed to identify several types of artifacts in diffusion data, including electromagneticinterference-likeartifact, regional signal loss, venetian blind artifact, inter-slice and intra-slice intensity artifact, and checkerboard artifacts. Tensor computation employed a weighted least square estimation to produce a diffusion tensor image (DTI) for each subject. Each DTI dataset was further assessed visually for artifacts with 3D Slicer (Fedorov et al., 2012) and was excluded if any artifact could not be corrected. The tensor eigenvalues were calculated to obtain diffusion property images of FA, AD, RD, and MD. Skull stripping was performed by propagating manual structural masks via deformable registration of a structural T2 weighted image to the corresponding B0 images. Atlases are available at https://www.nitrc.org/projects/macaque_atlas.

Longitudinal DTI atlas-based tract-profile analyses

An infant rhesus monkey longitudinal DTI atlas was built as described previously (Shi et al., 2017). Briefly, we employed the diffusion atlas building tool DTIAtlasBuilder (Verde et al., 2014) in a two-step approach, by first building the subject-specific atlases, one atlas per subject, which were then combined into an overall atlas. In each step, all corresponding FA maps were first intensity normalized and affinely co-registered. Then, an unbiased diffeomorphic FA atlas was created (Joshi et al., 2004). Subsequently, all the FA images were deformably registered to this diffeomorphic atlas with ANTS (Tustison et al., 2014). The final atlas was generated by averaging the deformed FA maps. The resulting deformation fields were then applied to each tensor image via finite-strain preservation. The final DTI atlas was computed as the average over all the warped tensor images. The deformation fields from the two steps were concatenated into a single final deformation field. This final deformation field allows the mapping of data to and from the longitudinal atlas space and the individual, native DTI space, and provides spatial normalization across all scans. To confirm that the registrations were successful two rounds of visual QC were performed. The first looked at all of the images overlaid on the atlas to capture any gross misalignments and errors. In the second round each subject's data were loaded into 3D Slicer (Fedorov et al., 2012) individually and assessed for alignment with the atlas.

We performed fiber tracking of major tracts in the longitudinal DTI atlas space with 3D Slicer, as described in Verde et al., 2014. ROI seeding voxels were manually determined and

standard streamline tractography was used to obtain major fiber tracts of interest, including the UF, MdLF, ILF, the genu and splenium (subdivided into occipital and temporal fibers) of the CC (Fig. 1A), as well as the fornix. Tracts were identified using rhesus monkey anatomical landmarks defined in previous publications (Schmahmann et al., 2007; Schmahmann and Pandya, 2009). Using the final deformation fields to warp the atlas fiber tracts into each subject's native DTI space, we sampled DTI tract profiles for FA, MD, RD, and AD at 0.3 mm intervals along each tract in native space. At every vertex, spaced at 0.3mm, each DTI metric is sampled with a Gaussian kernel along the fiber using a standard deviation of 1mm of the kernel (computed across the fibers in the tract) in the subject's native space, resulting in a fiber tract profile for that individual. Automatic profile quality assessment was performed by excluding subject data with correlation coefficients of less than 0.7 for each subject's FA tract profile with the average at each age independently (Verde et al., 2014). In previous studies of older macaques we applied a correlation coefficient threshold of 0.85 (Shi et al., 2013). To avoid erroneously discarding biologically relevant variability in the infant monkeys we applied the more relaxed threshold of 0.7. See Figure 2 for FA profiles of each tract across all five ages assessed (see Supplemental Material Figures 2,4,6, and 8 for plots of other metrics - RD, AD, MD). No significant differences were observed in the excluded data regarding early experience (i.e. infants reared by foster control or maltreating mothers) or biological mother using Chi-squared tests (see Supplemental Material for details).

Statistical analysis

Global (i.e. entire tract) and local (i.e. at each point along the tract profile) effects on FA were determined using the functional mixed effects model approach (FMEM) (Luo et al., 2015; Yuan et al., 2014). This approach allows the delineation of dynamic changes of diffusion properties with covariates of interest in a mixed effects model of spatially smoothing varying coefficient functions. The FA data are statistically functional data measured across tracts, as well as longitudinal data collected at multiple time points. FMEM allows the incorporation these two features in a unified model; that is, a functional mixed effects model. This method was specifically developed to address statistical properties of longitudinal neuroimaging data such that the statistical dependency due to within subject repeated measures (i.e. age; longitudinal analysis) and spatial location of the data along each tract (i.e. at every 0.3 mm intervals for this analysis) are included as random effects. Subject age was transformed using natural logarithms to produce roughly linear growth trajectories across the time period studied for use in the FMEM model (see Supplemental Materials for details regarding choice age transformation). An initial FMEM model that included all main and interaction effects for age (fixed and random effects), early maternal care experience (fixed effect), biological mother (fixed effect), sex (fixed effect), and social rank (fixed effect) was first applied. The model was then further refined by excluding those main effect and interaction terms that did not significantly ($p<0.05$) predict global FA of the tract using a backward elimination method. Because a threshold of 0.05 may be too stringent for model refinement, we also applied a threshold of 0.1, which resulted in the same final model. Cross-validation methods require considerable computational power, as we used an FMEM analysis (Yuan et al., 2014). For each of the fiber tracts and metrics, it sometimes takes several days to fit a model with high performance computing clusters. Thus, we were not

able to consider cross-validation methods. Furthermore, there exist no information criteria such as Akaike information criteria (AIC) or Bayesian information criteria (BIC) for FMEM. Thus, we applied a more traditional method, backward elimination. Three-way interactions were not considered as with only 181 scans in total, including all 42 subjects at all ages, we do not have sufficient sample size for models including three-way interactions. The model would have included more than 42 covariates because our data are longitudinal and statistically functional data; thus, another coefficient would need to be included for each vertex in the tract (e.g. for the occipital portion of the splenium this would be 219). We did attempt to fit a three-way interaction term, but the computation was not feasible for many fiber tracts due to ill-conditioned matrices. Even in cases where computation was possible, the result would be very unstable because of the small sample size and large number of terms. Thus, we decided to only consider two-way interaction terms. The final model included age, early experience (i.e. maltreatment), biological mother group, and an interaction term between early experience and biological mother group. Sex, social rank and their interaction terms were excluded because did they not show a significant effect on fiber tract properties. Global results were considered significant at $p<0.05$ using false discovery rate (FDR) corrected p-values. P-values were calculated using the wild bootstrap method as described in Yuan et al., 2014, and originally proposed by Wu (Wu, 1986). No cluster-based thresholding was applied for the atlas-based analyses.

Voxelwise WM skeleton analyses

An additional exploratory, voxelwise WM skeleton approach (Tract-based Spatial Statistics - TBSS, Smith et al., 2007) was also employed to complement the results of the atlas-based tract-profile approach. This voxelwise method of DTI analysis is unconstrained by *a priori* hypotheses and is less sensitive to registration errors. TBSS is robust to registration errors because local FA maxima are projected onto the WM skeleton, providing some flexibility to recover from registration errors. First, an average FA image was created from all subjects in the longitudinal atlas space described above, following previously published methods by our group (Howell et al., 2014). A skeletonized FA map representing the center of the WM was then calculated, and each individual subject's FA data was projected onto that skeleton to account for spatial variability between subjects as previously described (Smith et al., 2007). Because this method was specifically designed to be less sensitive to registration errors than the tract-based method, none of the animals defined as outliers above were excluded from the TBSS analysis, nor were any additional outlier detection methods applied, thus the entire sample as described in Table 1 was included. From here the skeletonized data was analyzed using the Multiscale Adaptive Generalized Estimating Equations (MAGEE, Li et al., 2013) framework to model both main and interaction effects of age (natural log of age in days), early experience, biological mother, sex, and social rank. This complete statistical model was refined by excluding main effect and interaction terms that did not significantly predict FA in any clusters. The final model included main effect terms of age, early maternal care experience (being raised by a control dam was assigned a value of 0), sex (females were assigned the value of 0), biological mother (biological infants of control dams were assigned a value of 0), and rank (high ranking animals were assigned a value of 0, middle ranking a value of 1, and low ranking a value of 2), and two interaction terms, 1) early experience by biological mother, and 2) early experience by rank. A cluster-based thresholding approach

based on random field theory (Worsley et al., 1996) using full width half mass (FWHM) of 1.5mm, p<0.01 as the significance threshold for cluster size, and p<0.05 as the significance level for individual voxels was applied. This method considers spatial dependencies between adjacent voxels and corrects for multiple comparisons. Tracts that were likely included in significant clusters were identified using published rhesus monkey white matter atlases (Adluru et al., 2012; Schmahmann and Pandya, 2009).

Results

Longitudinal DTI atlas-based tract-profile analyses

Tract-based analyses detected statistically significant global main effects of age in all tracts studied (UF, ILF, MdLF, CC genu/splenium, fornix, $p<10^{-20}$) (Fig. 3A). FA increased with age in all tracts (as shown in Figs. 1B and 2), whereas MD, RD, and AD decreased significantly across time in these tracts (see Fig. 1B and Figs. 2–4 in Supplemental Material). Significant global main effects of caregiving were also detected in bilateral MdLF (left, p=0.01; right, p<0.001), and the right ILF (p=0.05) (Fig. 3B), with maltreated animals showing reduced FA in these tracts across all ages studied (from 2 weeks through 18 months). Trends towards interactions between early caregiving experience and biological mother effects were also suggested in all of these tracts, with animals born to control mothers and cross-fostered to control mothers showing the highest FA values, although they failed to reach statistical significance (left MdLF, p=0.09; right MdLF, p=0.08; right ILF, p=0.09) (Fig. 3C). Local results show that the significant global main effects of early caregiving experience were due to group differences in FA in the center of the tracts, where the tracts are most coherent. There were no other significant main or interaction effects detected in the left ILF, the CC (genu or splenium subdivisions) or bilateral fornix.

Exploratory voxelwise WM skeleton TBSS analyses

A voxelwise analysis was applied in a WM skeleton to identify regions outside of the *a priori* tracts examined in the tract-profile analysis that may be sensitive to early experience, heritable factors, and individual subject characteristics including sex and social rank.

Main effects of age—Forty-eight clusters showed a significant age effect (Table 1, Fig. 4), most of them showing increasing FA with increasing age, while a single cluster located in the dorsal aspect of the bilateral fornix showed decreasing FA with age. No interaction effects with age were detected.

Main and interaction effects of early caregiving experience—Significant main effects of early maltreatment experience were detected in three clusters, two bilateral clusters in the extreme capsule (EC, Table 2, Fig. 5A) and one in the left posterior limb of the internal capsule (PLIC, Table 2, Fig. 5B) (Schmahmann et al., 2007; Schmahmann and Pandya, 2009). Based on their anatomical location the EC clusters likely include parietal and temporal fibers (Mars et al., 2016; Schmahmann and Pandya, 2009). The PLIC cluster likely contains sensorimotor fibers, including a portion of the corticospinal tract (Schmahmann and Pandya, 2009). In all three of these clusters positive beta values from the fitted model indicate that maltreated infants have higher FA than infants that experienced competent,

control, care. However, because significant interactions between experience and biological mother, and experience and social rank were also identified in these same regions (see below) it is not possible to interpret this main effect for either group without considering the interaction effects with biological factors and social rank.

Two clusters with significant interactions between early caregiving experience and biological dam were found, one in the left superior longitudinal fasciculus, SLF (Table 2, Fig. 5C), and the other in the left MdLF (Table 2, Fig. 5D), in agreement with the findings reported above as part of the longitudinal DTI atlas-based tract-profile analysis. We investigated this interaction further by testing whether animals that were fostered to a dam with matching biological maternal care (i.e. control-control - CC, maltreating-maltreating - MM) were significantly different from those fostered to a dam with a different (mismatched) pattern of maternal care (i.e. control-maltreating - CM, maltreating-control - MC). We found that animals fostered to a dam with the expected caregiving behavior (matched) had significantly higher FA in these regions (Table 3, Fig. 6) than those fostered to a dam with a different maternal care pattern (mismatched).

One cluster with a significant interaction between early caregiving experience and social rank was detected in a region of WM that may include the right EC, or portions of the internal capsule (IC; Table 2, Fig. 5E). The negative coefficient value for this interaction from the fitted model suggests that as social rank increases, the FA values of animals raised by maltreating dams decreases incrementally as compared to animals raised by control dams. No other interactions with early caregiving experience were found.

Main effects of biological dam—No clusters with significant main effects of biological dam were found.

Main effects of sex—Two clusters with statistically significant main effects of sex were found: one in the left PLIC and the other in the isthmus of the CC (temporal and parietal fibers) (Table 2, Fig. 7). The negative beta values from the fitted model suggest that males have lower FA in these regions than females during this developmental period (from 2 weeks through 18 months). No significant interaction effects with sex were found.

Main effects of social rank

Two clusters with statistically significant main effects of social dominance rank were found in a bilateral region that is likely to contain the IC and/or the EC (Table 2, Fig. 8). The positive beta values from the fitted model indicate that FA in these regions increases with social rank for biological infants of control dams. No other significant interaction effects besides those previously reported with early caregiving experience were detected.

Discussion

In this study we examined the developmental changes in major primate brain tracts from infancy through the juvenile period and how maternal care and biologically heritable factors shape their developmental trajectories. For this, we studied the effects of infant maltreatment on development of brain WM microstructural integrity as quantified by FA throughout

infancy and into the juvenile period using a cross-foster design to disentangle the effects of early maternal care from those of heritable factors in a naturalistic rhesus monkey model. We used *in vivo* DWI to approach this question in two ways, (1) using an atlas-based tract-profile approach in which we investigated specific impacts on cortico-limbic tracts, and (2) an exploratory voxelwise strategy in which no *a priori* WM regions were identified. Using the atlas-based method we detected significant global effects of age on all WM tracts examined (bilateral UF, bilateral fornix, bilateral MdLF, bilateral ILF, and the genu and splenium of the CC), with FA increasing in all tracts across this developmental period. Global main effects of early experience (i.e. competent caregiving versus maltreating caregiving) were detected in both right and left MdLF and the right ILF, with lower FA in maltreated animals as compared to control animals. Interestingly, FA was higher in these WM tracts in animals fostered to a dam with a "matching" biological maternal care pattern as compared to animals raised by a dam with the opposite caregiving pattern (e.g. mismatched). Exploratory voxelwise analyses modeled the effects of not only age, maltreatment experience, and biological mother as in the tract-profile analyses, but also included the effects of sex and social rank to provide an exploratory view into other individual biological characteristics and social experiences that may affect WM development across the entire primate brain. This exploratory analysis paralleled the tract-based analyses by demonstrating that most brain regions increased FA with age. It also confirmed the impact of infant maltreatment on ILF and MdLF, although effects on additional regions were uncovered. Main effects of sex and social rank were also identified in additional WM regions (e.g. the internal capsule and the CC), as were areas where biological mother and social rank interacted with early experience to predict FA.

To our knowledge, this is the first report of longitudinal WM development, from infancy to the juvenile period (2 weeks to 18 months of age), in the nonhuman primate brain. The positive relationship between FA and age found in both the longitudinal DTI atlas-based tract-profile analyses and the voxelwise analyses is consistent with several previous studies of WM development in both humans (Deoni et al., 2012, 2011; Dubois et al., 2014; Geng et al., 2012; Huang et al., 2006) and older, juvenile and adult macaques (Knickmeyer et al., 2010; Kubicki et al., 2018; Shi et al., 2013), as well as *post mortem* studies (Brody et al., 1987; Huang et al., 2006; Kinney et al., 1988; Yakovlev and Lecours, 1967). This increase in FA with age is thought to be due to changes in WM microstructural architecture (i.e. increased axonal packing, organization and diameter, and myelination) that result from a combination of cellular processes that occur throughout WM development (Concha, 2014; Walhovd et al., 2014). This increase in microstructural integrity is thought to lead to subsequent increases in the speed of action potential impulse propagation between regions that come with strengthening of connections (Beaulieu, 2014). Many recent studies have suggested that increases in FA are related to improved performance on tasks providing evidence that experience-related changes in WM are meaningful for behavior (Fields, 2010, 2008). Thus WM development creates both a period of increased adaptability and plasticity of the developing brain to response to early experiences, as well as vulnerability to environmental insults, including stress (Andersen, 2003; Fox et al., 2010; Lupien et al., 2009).

Studies of early life stress in humans and other primate species have identified several brain WM tracts that are sensitive to adversity (De Bellis et al., 1999)(Hanson et al., 2013; Brittany R. Howell et al., 2013; Howell et al., 2014; McCrory et al., 2012; Ohashi et al., 2017; Teicher et al., 2003). For example, studies investigating the effects of institutional rearing and social deprivation on WM in humans have reported decreased FA in prefrontal WM tracts including the UF, which connects the prefrontal cortex with temporal regions such as the amygdala (Eluvathingal et al., 2006; Govindan et al., 2010). Child neglect has also been linked to decreases in the structural integrity of prefrontal WM (Hanson et al., 2013). In the current study, as well as in previous work by our group using the same rhesus monkey model of maltreatment (Brittany R. Howell et al., 2013), however, we failed to detect a significant effect of infant maltreatment experience on the UF, despite robust effects on other brain tracts, such as the ILF, connecting temporal regions with occipital cortex, and the MdLF, connecting temporal regions with inferior parietal cortex. Our findings are consistent with other work, including a recent study of WM in adolescents with histories of child maltreatment that reported several WM tracts affected by maltreatment, including lower FA in bilateral superior longitudinal fasciculus, the right cingulum bundle, the left inferior fronto-occipital fasciculus, and the splenium of the CC, but not the UF (Huang et al., 2012). Our findings also support recent work that identified effects of maltreatment on WM in similar regions using a network approach (Ohashi et al., 2017). The discrepancy between reports in the literature could be due to specific WM effects of different types of early adverse experience (e.g. maternal deprivation, institutional rearing, maltreatment), developmental timing, or duration and severity of the experience. However, in the current study we did detect effects of early experience on the MdLF, which also contains prefrontal fibers (Petrides and Pandya, 2009; Schmahmann et al., 2007; Schmahmann and Pandya, 2009), and may suggest some common regional effects on WM development across different forms of early life stress.

The MdLF is a long association tract connecting high-level association areas and paralimbic cortices including the inferior parietal lobule, the parahippocampal gyrus, the cingulate gyrus, and the prefrontal cortex (Schmahmann et al., 2007; Schmahmann and Pandya, 2009). Based on the cortical regions connected by the MdLF it is likely that this tract plays an important role in communication, particularly via integration of information regarding spatial organization and motivational valence. The function of the MdLF in primates is unclear, but there is recent evidence that it is involved in social learning, particularly imitation in adult humans, but not adult macaques (Hecht et al., 2013). Although adult macaques do not imitate, infant macaques do (Ferrari et al., 2006). Recent work looking at imitation in infant rhesus monkeys suggests that social experience in the form of maternal care during the first days of life leads to a sensitization of the infant to social cues (Vanderwert et al., 2015). The findings from the current study are consistent with this literature, as they both highlight the importance of early experience, especially maternal care, on brain WM. They also suggest that these alterations may be related to the social deficits often observed in children with histories of maltreatment. Future studies are required to determine the functional role of this tract in behavior across development.

In addition to alterations in the MdLF, maltreatment was also associated with lower FA in the ILF. The ILF is also a long association tract that connects occipital and temporal cortices

(Ashtari, 2012; Schmahmann et al., 2007; Schmahmann and Pandya, 2009). In humans there is evidence that the ILF shows functional lateralization, with the left tract being important for language processing (Ivanova et al., 2016), and the right being important for face perception (Rokem et al., 2017) and recognizing emotional facial expressions (Philippi et al., 2009; Unger et al., 2016). Because macaques use facial expression to learn about the state of conspecifics alterations in this WM bundle may result in deficits in social interactions.

Many conditions and processes have been associated with alterations in the ILF (Chanraud et al., 2010). One study of children that had experienced neglect early in life also detected decreased FA in the ILF, with those with lower FA having poorer performance on a spatial planning task (Hanson et al., 2013). In another form of early life adversity, adults with histories of witnessing domestic violence in childhood had decreased WM volume in the ILF (Choi et al., 2012). In addition to these studies of specific early life stresses, decreased FA in the ILF has also been related to schizophrenia (Pérez-Iglesias et al., 2010), with FA in the right ILF being negatively associated with thinking disorder (Phillips et al., 2009). A recent study of adult schizophrenic patients with histories of child maltreatment detected a negative association between scores on the Risky Family Questionnaire (a standardized measure of adverse childhood experience) in the left ILF (Poletti et al., 2015). This work highlights the role that early experience plays in the etiology of psychopathology. Wolff and colleagues reported increased FA in the left ILF in 6-month-old human infants that went on to develop autism spectrum disorder (Wolff et al., 2012). This pattern of increased FA continued through 12 months, but by 24 months the children with autism showed decreased FA in this tract as compared to controls (Wolff et al., 2012). Other groups have found similar differences between autistic individuals and those without a diagnosis, with decreases in FA being reported in adults and adolescents (Bloemen et al., 2010; Groen et al., 2011; Kleinhans et al., 2012). These studies combined with the results of the current study suggest that experience related alterations in WM development of the MdLF and ILF may contribute to the behavioral alterations and increased risk for developing psychopathology, particularly psychopathologies involving alterations in social behavior and communication. Nearly significant global maltreatment by biological mother interaction effects were identified in these tracts as well (bilateral MdLF and right ILF), suggesting that heritable factors may also play a modulatory role on the effects of early experience on temporal WM development; however, this hypothesis needs to be addressed by future studies utilizing larger sample sizes.

Voxelwise analyses using the TBSS method corroborated most of the maltreatment experience related effects, but also identified additional WM regions that were sensitive to early life adversity, biological mother, sex and social rank. Before discussing these results it is important to acknowledge that the TBSS method has limitations in regards to identifying specific tracts due to how wide regions of WM that contain multiple tracts are simplified into a single-voxel wide WM skeleton. Despite this limitation, this approach was chosen as an exploratory method to identify additional WM regions where FA was affected by early maternal care experience and other factors to complement the specific tract-based approach taken above due to several key advantages. One benefit of this method is that it limits the number of statistical tests necessary for voxelwise analysis of WM, thus making this type of

exploratory analysis more tractable statistically by reducing false positives. It is also less sensitive to registration errors.

Main effects of maltreatment experience, sex, and social rank were also found in a WM region that based on its anatomical location contains either the PLIC and/or the extreme capsule (EC). The PLIC contains fibers that connect superior temporal and parietal cortices with subcortical regions including the thalamus, as well as fibers of the corticospinal tract that carry information from primary motor cortex to motor neurons in the spinal cord (Schmahmann and Pandya, 2009). The functional role of the fibers of the PLIC is strongly involved in voluntary motor control based on studies of both healthy participants (Kim et al., 2008) and stroke patients (Pendlebury et al., 1999), as well as multiple sclerosis patients (Lee et al., 2000). Reduced FA in PLIC has been associated with motor impairments (Puig et al., 2011; Sach et al., 2004). The EC is a long association fiber that connects the rhesus cytoarchitectural equivalents of Wernicke's and Broca's areas in humans, suggesting a role for this WM bundle in communication in monkeys (Petrides and Pandya, 2009, 2007). It is interesting to note that fibers arising from the orbitofrontal cortex course through the EC before joining the MdLF (Schmahmann and Pandya, 2009), making it possible for the effects in this region identified using a voxelwise approach to be related to the tract-based findings in the MdLF discussed previously. The main effect of maltreatment described by the voxelwise analysis shows a positive relationship between FA in this region of WM and maltreatment. Other studies of the effects of early life adversity have also reported differences in similar regions (Choi et al., 2009), although the experience of ELS was related to decreases in FA in these WM regions. Interestingly, Frodl and colleagues reported increased FA in several WM regions in unaffected first-degree relatives of those diagnosed with major depressive disorder that had experienced high levels of early life adversity (Frodl et al., 2012). This suggests that increased FA may contribute to resilience in the face of ELS. One study investigating the effects of a neonatal intervention focused on supporting the development of the infant in the context of the family reported increased relative anisotropy (a measure closely related to FA) in the left internal capsule, an increase that was related to decreased reactivity (Als et al., 2004), supporting the role of increased WM structural integrity in this region in resilience in the face of ELS.

In addition to the main effect of sex found in the left PLIC, a main effect of sex was also found in the isthmus of the CC, consistent with other studies investigating sex differences in the CC (Aboitiz, Francisco; Rodriguez, Eugenio; Olivares, Ricardo; Zaidel, 1996). Sex effects on the volume and surface area of this portion of the CC have been reported previously with females having larger surface areas in this region (Steinmetz et al., 1992; Witelson, 1989), although not all reports are consistent (Bishop and Wahlsten, 1997; Giedd et al., 1999). In addition to these sex dependent differences in size, sex differences in rates of development during childhood and adolescence have also been reported (Luders et al., 2010). The isthmus of the CC carries interhemispheric fibers of parietal and superior temporal origin (Hofer and Frahm, 2006; Schmahmann and Pandya, 2009; Witelson, 1989). In humans these regions are thought to be involved in auditory processing and speech production (Dougherty et al., 2007; Westerhausen et al., 2009). A recent study reported a relationship between structural development of the isthmus of the CC and speech processing in 6 to 8-year-old children (Westerhausen et al., 2011).

In addition to the main effect of social rank detected in the IC, interactions with maltreatment experience were identified in several other WM regions including the ILF, SLF, and the corticospinal tracts. In these regions FA decreased incrementally with decreasing rank in maltreated animals. Interestingly, in a previous study of WM in animals that received normative care our group identified similar regions with rank dependent levels of FA (Howell et al., 2014), however FA was increased in these regions in low ranking animals. The results from the current investigation suggest that maltreatment may be more detrimental in low ranking animals. They also highlight the need to consider the interactions between social hierarchy status (i.e. social dominance ranks in monkeys, and potentially socioeconomic status in humans) and early experience when investigating the effects of early experience on brain development.

The interaction between maltreatment experience and biological dam detected in the TBSS analysis provides empirical evidence supporting the environmental match/mismatch hypothesis, as opposed to the cumulative stress hypothesis. In the cumulative stress model, chronic exposure to stress early in life is thought to have an additive effect on poor outcomes (Taylor, 2010). In contrast, the match/mismatch hypothesis posits that offspring phenotypes that match those of previous generations (due to genetic or potentially epigenetic factors) confer some adaptive outcomes to the ancestral environment, including early social environment (Del Giudice et al., 2011; Ellis and Boyce, 2008; Nederhof and Schmidt, 2012). This view has been used to explain the link between early life stress and psychopathology considering individual variability in vulnerability and resilience, leading to the mismatch hypothesis of psychiatric disorders such as depression (Nederhof and Schmidt, 2012; Santarelli et al., 2014). In the current study infants raised by foster dams that "matched" the maternal care pattern of their biological dams had higher FA in specific WM regions than infants with mismatched maternal care. These findings are consistent with reports from studies in other animal models (Daskalakis et al., 2012; Nederhof and Schmidt, 2012; Santarelli et al., 2014) and highlight the need to consider ancestral experiences and heritable factors in conjunction with postnatal experience when trying to understand the complex outcomes of early life adversity.

It is important to acknowledge the limitations of the current study. While the sample size used was large for a macaque study and provided enough power to fit the models presented using a longitudinal design and appropriate multiple comparison corrections, it was not large enough for additional analyses to investigate the consequences of brain WM developmental differences on behavior, or to examine potential stress-related biological mechanisms (i.e. stress hormones). Additional limitations include: (1) the moderate resolution of the DTI data, (2) the deterministic methodology used to track the major WM tracts in the DTI atlas (which does not allow for modeling of crossing fibers), both of which limit our ability to accurately delineate tracts in regions with extensive crossing fibers (i.e. thalamic radiations, superior longitudinal fasciculus), and (3) the repeated exposure to anesthesia, which has been shown to affect oligodendricites in young monkeys (Brambrink et al., 2012; Noguchi et al., 2017; Schenning et al., 2017), could potentially affect the measures of white matter development studied here, although this is the case across all groups. Despite these limitations, the current study uncovered important normative developmental trajectories of NHP brain WM, as well as the role of early adversity-related impact on brain WM

development, and sets the stage for future studies specifically designed to address those questions.

Conclusions

The results of the current study provide a possible neurobiological mechanism through which adverse early experiences result in alterations in behavior. The alterations in WM development reported here are in regions known to support social brain functioning, supporting a putative role of these alterations in brain WM in the behavioral outcomes associated with early life stress. These effects were found in regionally specific areas, showing that early life stress does not affect brain WM in a nonspecific, or global, manner. Effects were not identified in only WM tracts known to be important for emotional, stress and social regulation, such as the UF, which suggests that a more complex network of brain regions and alterations underlie the long-term outcomes of maltreatment. These results parallel resting state functional imaging studies that show alterations in functional connectivity in the default mode network, including important association regions such as the parietal cortex, one of this network's major hubs. There were no caregiving by age interactions, meaning that early experience did not affect growth trajectories, but the overall WM tract integrity (FA magnitude) throughout infant and juvenile development was affected in specific regions beginning very early in life. Modulation of the effects of early experience by heritable factors was also found in the voxelwise analyses, emphasizing the additional evolutionary importance of current maternal care and ancestral experience in guiding offspring development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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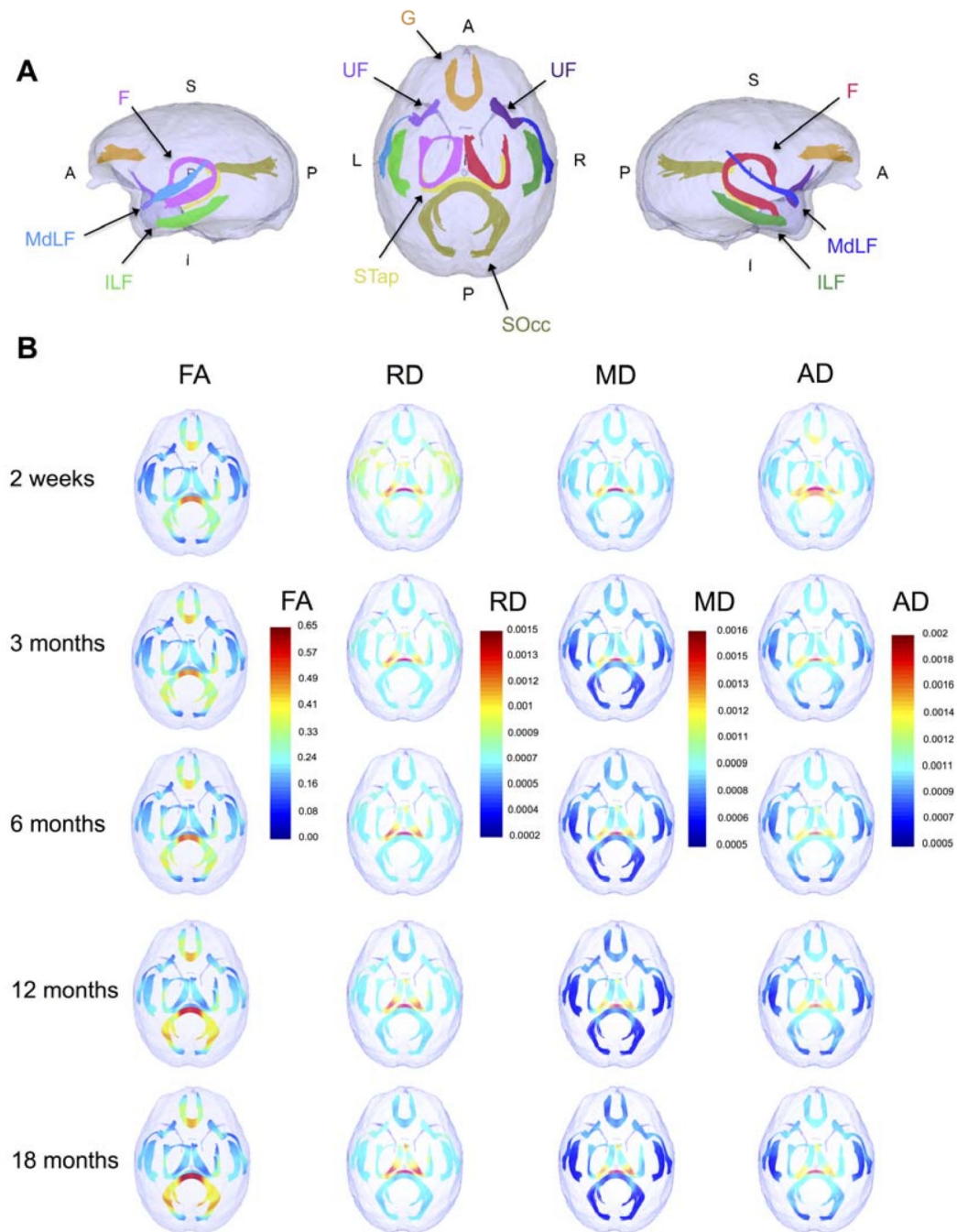
Figure 1:

(A) Tracts in the longitudinal DTI atlas included in tract-based analyses. Orange = genu of the corpus callosum (G), Purple = right uncinate fasciculus (UF), Lavender = left uncinate fasciculus (UF), Red = right fornix (F), Pink = left fornix (F), Dark blue = right middle longitudinal fasciculus (MdLF), Light blue = left middle longitudinal fasciculus (MdLF), Dark green = right inferior longitudinal fasciculus (ILF), Light green = left inferior longitudinal fasciculus (ILF), Yellow-green = splenium of the corpus callosum (SOcc), Yellow = temporal corpus callosum fibers (STap). **(B) FA, RD, MD, and AD values at each**

age of assessment. Metric values increase from blue to red. Position key: I = inferior, S = superior, R = right, L = left, A = anterior, and P = posterior.
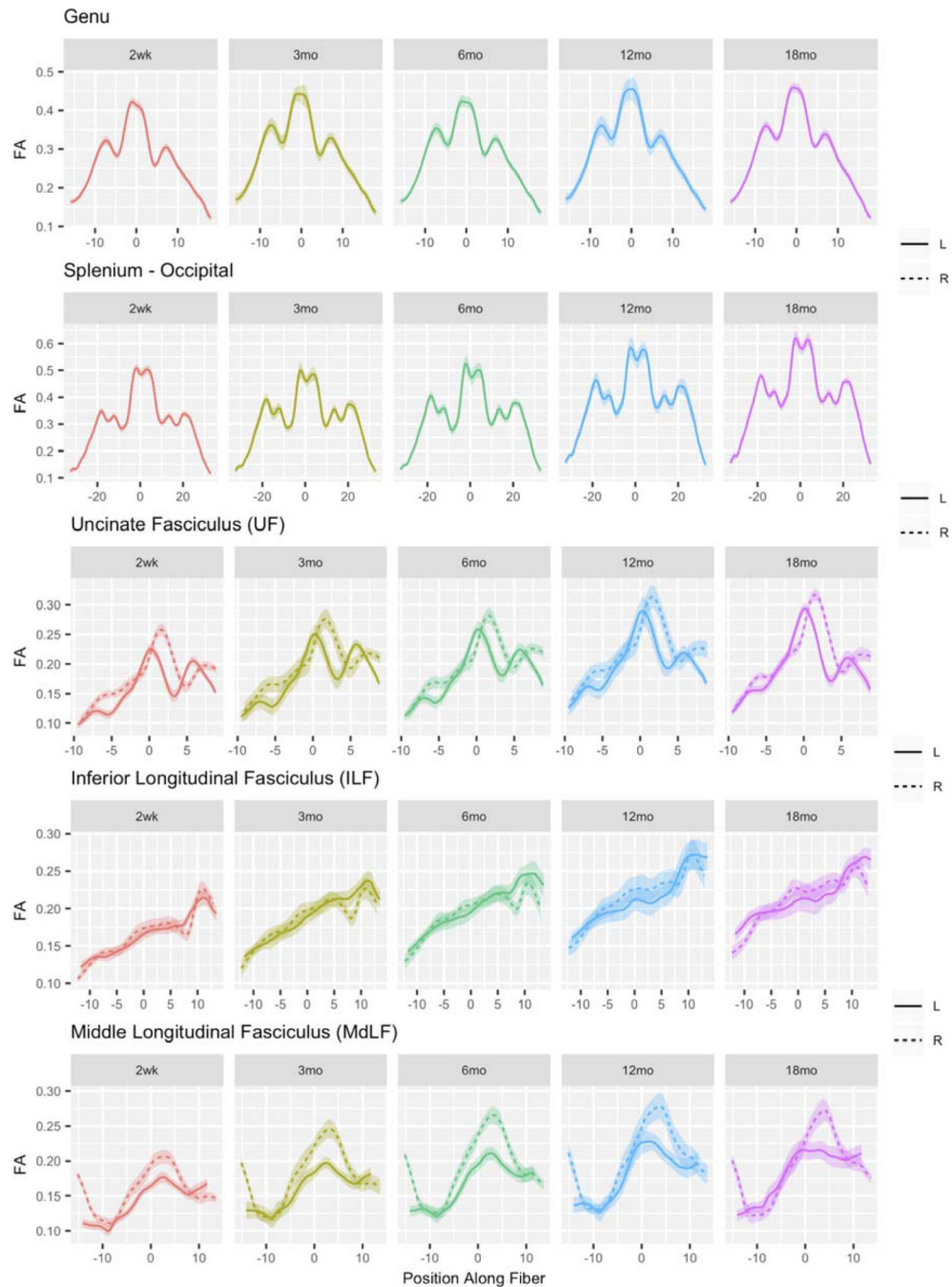
Figure 2: FA values plotted across the spatial extent of each tract across all ages of assessment.
The position along the tract is given in 0.3mm intervals where 0 is the center of the length of the tract, and positive values represent the anterior aspect of the tract, or the right side of the tract if the tract is interhemispheric.
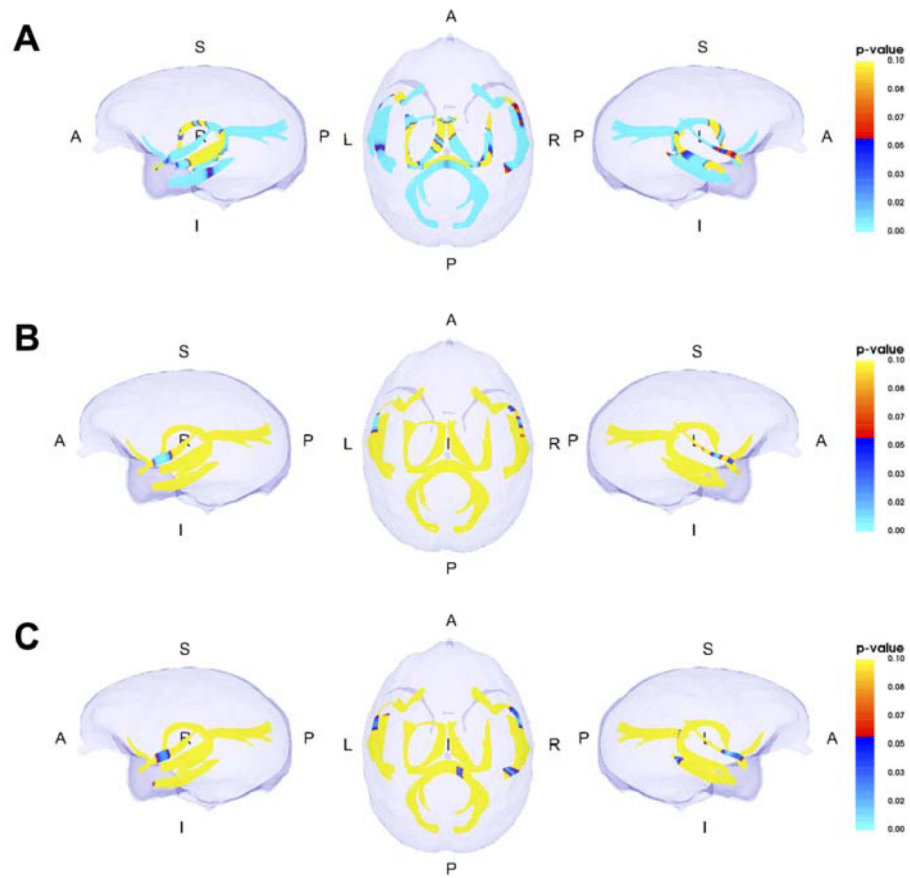
Figure 3: Longitudinal DTI atlas-based tract-profile analyses:
(A) local results of main effects of age, (B) local results of main effects of maltreatment experience, (C) local results for maltreatment experience by biological dam interaction effects. Color indicates local FDR corrected p-value. Position key: I = inferior, S = superior, R = right, L = left, A = anterior, and P = posterior.
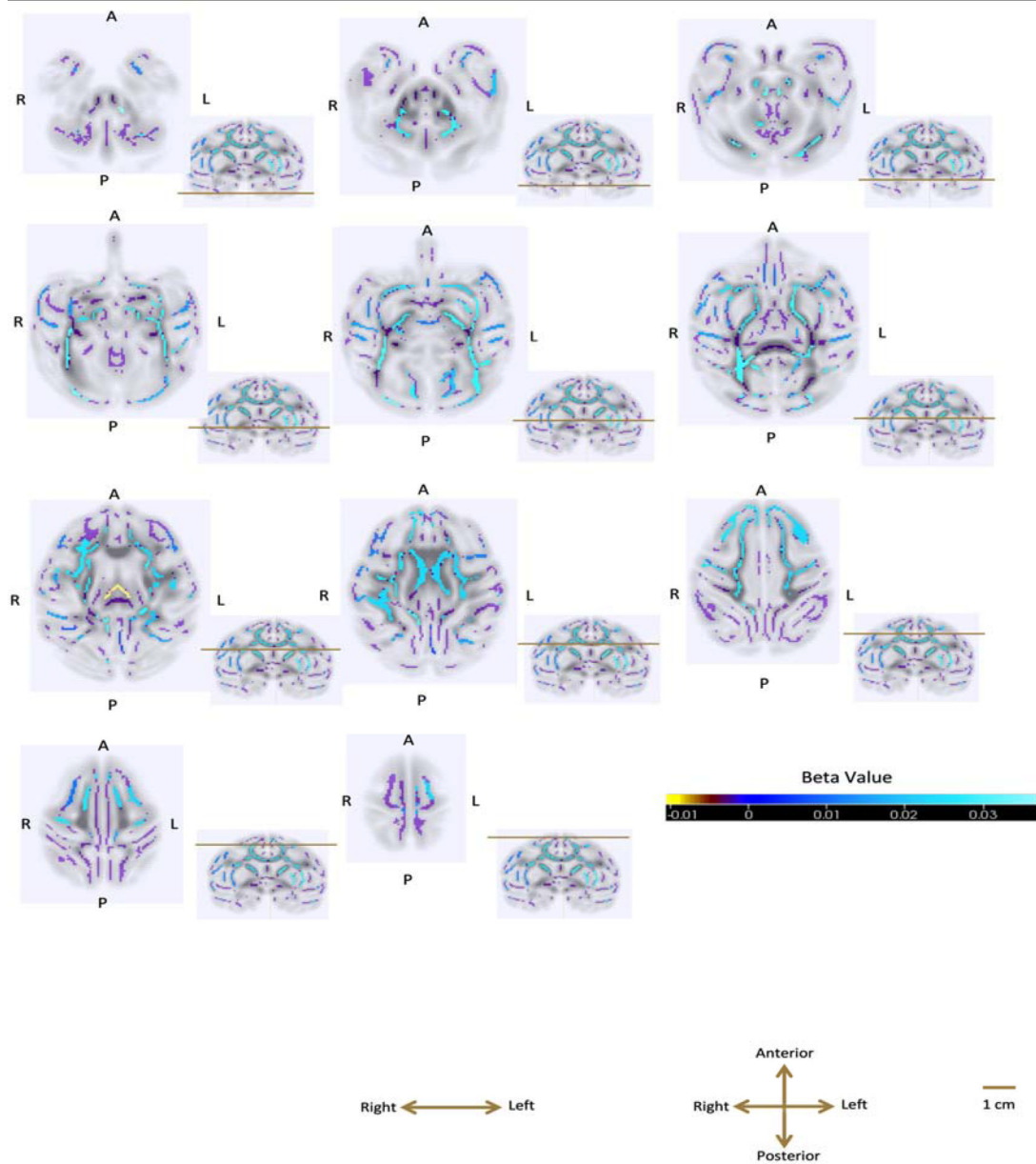
Figure 4: TBSS analysis: Main effects of age.
Green voxels indicate the FA skeleton produced as part of the TBSS analysis. Other colored voxels represent the beta-value from the fitted model where statistically significant clusters (thresholded at p<0.01 for cluster size and p<0.05 for individual voxels to correct for multiple comparisons) were detected. Position key: I = inferior, S = superior, R = right, L = left, A = anterior, and P = posterior.
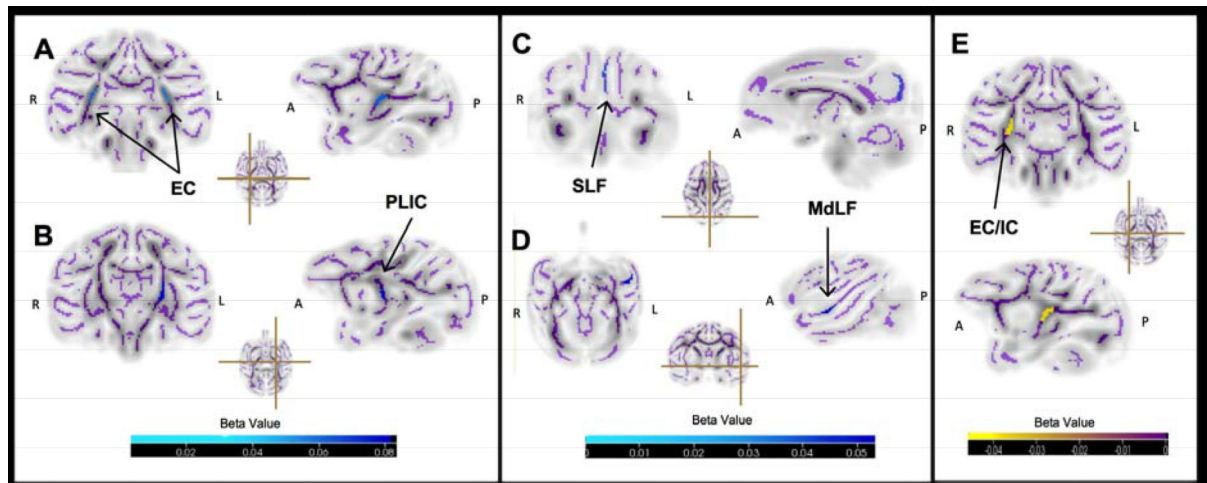
Figure 5: TBSS analysis: Main and interaction effects of early caregiving experience.
Green voxels indicate the FA skeleton produced as part of the TBSS analyis. Other colored voxels (red-yellow-blue scale) represent the beta-value from the fitted model where statistically significant clusters (thresholded at p<0.01 for cluster size and p<0.05 for individual voxels to correct for multiple comparisons) were detected. Main effects of early caregiving experience were found in (A and B) bilateral extreme capsule (EC) and the left posterior limb of the internal capsule (PLIC). Interaction effect between early caregiving experience and biological dam were found in (C) the superior longitudinal fasciculus (SLF) and (D) the middle longitudinal fasciculus (MdLF). Interaction effect between early caregiving experience and social rank found in (E) the internal capsule. Position key: I = inferior, S = superior, R = right, L = left, A = anterior, and P = posterior.
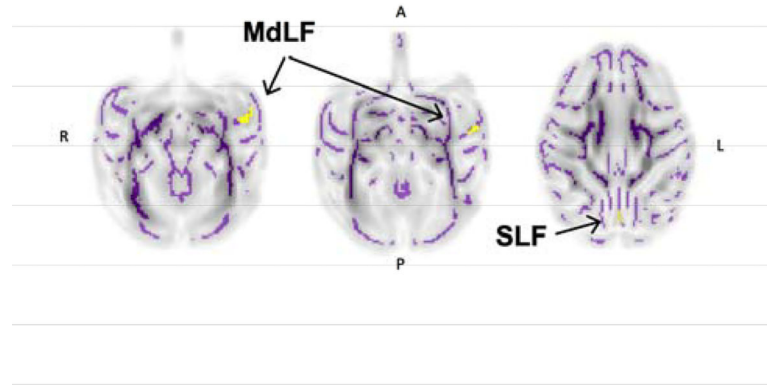
Figure 6: TBSS analysis: Contrast of animals raised by dams with maternal behavior patterns similar to their biological dams (i.e. matched) versus animals raised by dams with the opposite behavior pattern (i.e. mismatched).

Green voxels indicate the FA skeleton produced as part of the TBSS analysis. Blue voxels represent where mismatch animals had significantly (p<0.01 for cluster size and p<0.05 for individual voxels) lower FA than matched animals (the left middle longitudinal fasciculus, MdLF, and the left superior longitudinal fasciculus, SLF). Position key: I = inferior, S = superior, R = right, L = left, A = anterior, and P = posterior.

Figure 7: TBSS analysis: Main effect of sex.
Green voxels indicate the FA skeleton produced as part of the TBSS analysis. Other colored voxels represent the beta-value from the fitted model where significant clusters (thresholded at p<0.01 for cluster size and p<0.05 for individual voxels to correct for multiple comparisons) were found. Position key: I = inferior, S = superior, R = right, L = left, A = anterior, and P = posterior.
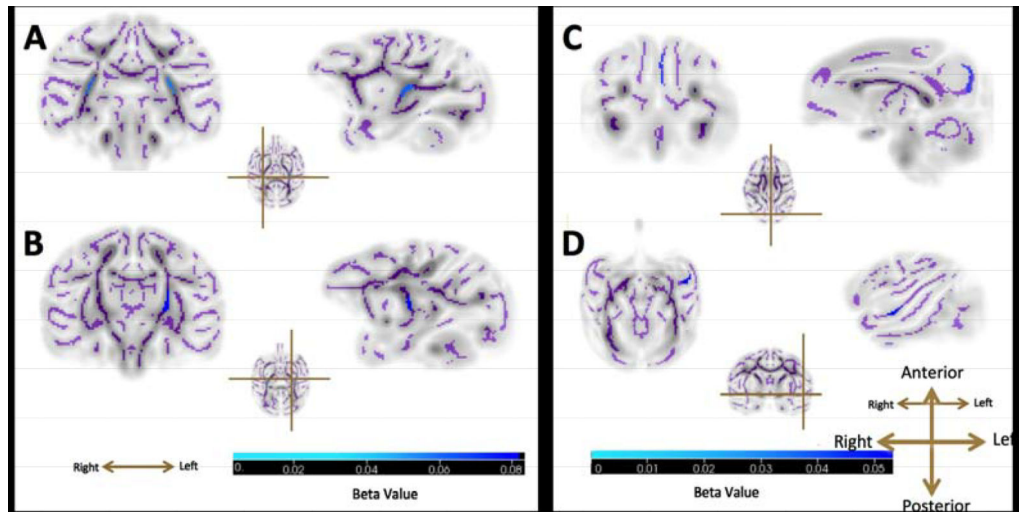
Figure 8: TBSS analysis: Main effect of social rank.
Green voxels indicate the FA skeleton produced as part of the TBSS analysis. Other colored voxels represent the beta-value from the fitted model where significant clusters (thresholded at p<0.01 for cluster size and p<0.05 for individual voxels to correct for multiple comparisons) were found. Position key: I = inferior, S = superior, R = right, L = left, A = anterior, and P = posterior.
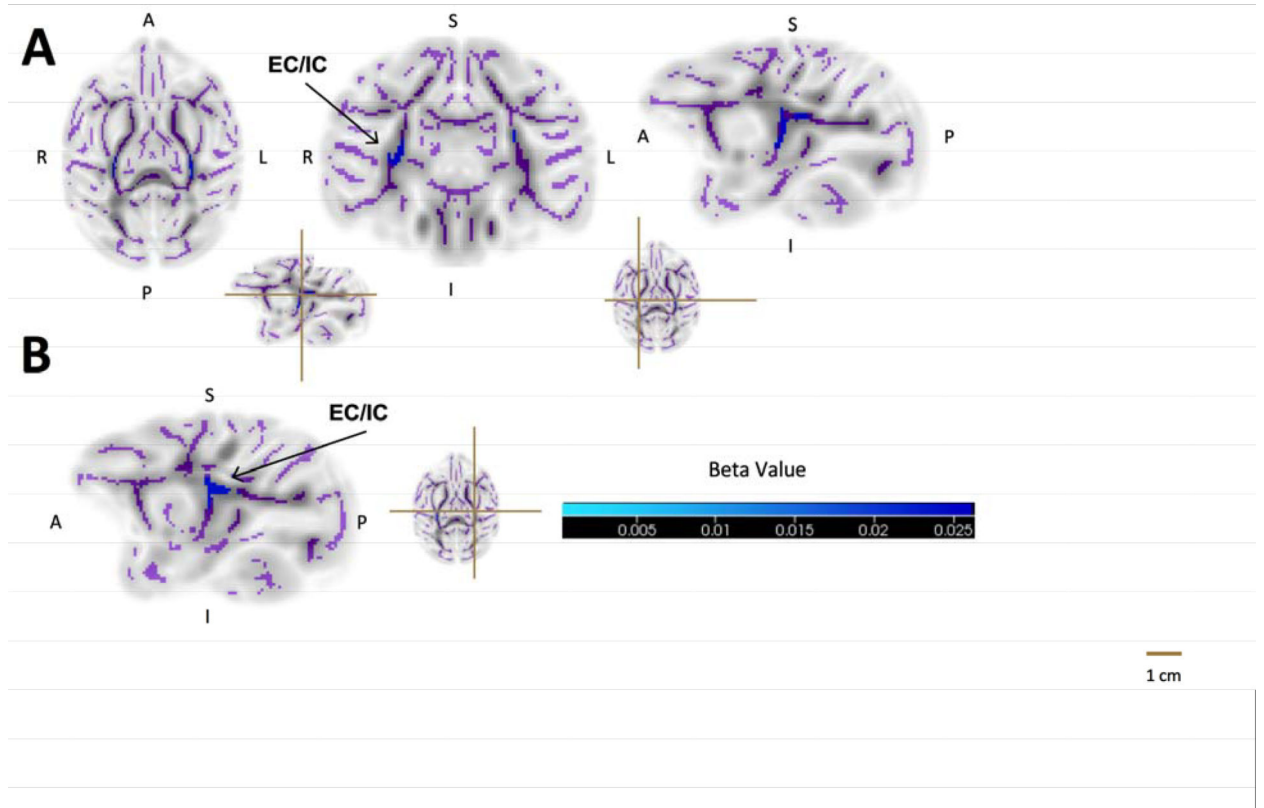
Table 1:

TBSS analysis table: Main effect of age.

Cluster	Size (voxels)	p-value	Average Beta from Fitted Model	White Matter Region
1	2628	$< 10^{-20}$	0.024449	R-PLIC, R-ALIC, R-EC, R-SCR, R-CP, R-ST, R-VPF, R-ACg-WM, R-IFG-WM, BCC, R-MB-WM
2	2198	$< 10^{-20}$	0.022143	L-ST, BCC, L-ACR, L-DPF, R-SLF, R-EC, L-ALIC, R-ALIC, L-PLIC, L-EC, L-ACg-WM, R-ACR, L-OC, R-IFG-WM, L-PCR, R-ALIC, R-MB-WM, R-CST
3	1701	$< 10^{-20}$	0.027713	L-CST, L-CP, L-ST, L-PLIC, L-ALIC, L-EC, L-SLF, L-DPF, L-SCR, BCC, L-MB-WM,L-DPCR
4	782	$< 10^{-20}$	0.02952	L-RLIC, L-PTR, L-EC, L-PLIC, L-TAP, R-DPCR, R-RLIC, R-PTR, L-SS, L-MB-WM, Splenium
5	618	$< 10^{-20}$	0.019205	L-EC, L-SLF, Splenium, L-DPCR, R-DPCR, L-PCR, L-CgC, R-PCR, R-PCR, R-PTR
6	367	2×10^{-12}	0.014671	Splenium, L-PCR, L-DPCR, CgC-L, L-SLF, L-STG-WM
7	331	1×10^{-11}	0.015353	R-STG-WM, L-STG-WM, R-EC, L-EC
8	319	3×10^{-11}	0.019004	L-PTR, R-EC, R-STG-WM
9	304	1×10^{-10}	0.011702	L-ACR, L-PTR, L-IFG-WM
10	284	3×10^{-10}	0.027434	L-IFG-WM, L-ACR, L-OC, L-ICP, MCP
11	267	1×10^{-9}	0.025582	L-ICP, R-SCP, R-ICP, MCP, L-OC
12	255	2×10^{-9}	0.015338	R-ICP, R-OC, R-SLF
13	247	4×10^{-9}	0.011445	R-SLF, R-IFG-WM, R-ACR
14	244	5×10^{-9}	0.022957	Genu, R-IFG-WM, L-DPF, BCC
15	229	1×10^{-8}	0.01971	BCC, L-ACR, R-ACR, Genu
16	190	2×10^{-7}	0.014508	L-MTG-WM, R-MTG-WM, L-SS
17	184	3×10^{-7}	0.013335	R-MdLF
18	172	9×10^{-7}	0.033744	R-MdLF, R-Occipital WM
19	163	0.000002	0.02644	R-PCR, R-PTR, R-Occipital WM
20	153	0.000004	0.014867	R-PCR, L-MdLF
21	151	0.000005	0.01339	L-SS, L-MdLF
22	148	0.000007	0.017619	R-SS, R-MTG-WM, L-UF
23	131	0.000027	0.016157	L-PCR, R-MTG-WM, R-SS
24	120	0.000069	0.032015	L-PCR, L-MB-WM, R-MB-WM, R-SCP, L-SCP, L-CTG, R-CTG
25	105	0.000263	0.013821	R-CTG, L-CTG, R-SCP, L-SCP, R-EC
26	104	0.000289	0.027644	R-EC, L-SLF, L-PTR, L-SS, L-MTG-WM
27	103	0.000316	0.006434	L-DPCR, L-PTR, L-SLF, L-MTG-WM
28	102	0.000346	0.022481	L-DPCR, R-SLF
29	102	0.000346	−0.011344	R-SLF, BCC, Fornix
30	100	0.000417	0.013708	BCC, R-UF, Fornix
31	97	0.000551	0.015296	L-SCR, R-UF
32	95	0.000664	0.010236	L-SS, R-DPF, L-SCR
33	90	0.001067	0.013451	L-IFG-WM, R-SCR, L-SLF
34	79	0.003126	0.011282	L-IFG-WM, R-MB-WM
35	77	0.003821	0.012316	R-SCR, R-MB-WM

Cluster	Size (voxels)	p-value	Average Beta from Fitted Model	White Matter Region
36	74	0.005178	0.012141	R-SCR
37	74	0.005178	0.022472	L-SLF, R-SLF
38	72	0.006355	0.016477	L-SLF
39	70	0.007813	0.012757	R-EC, R-PCR
40	69	0.008668	0.030249	R-EC
41	67	0.010686	0.009406	R-VPF, R-Occipital WM, R-UF
42	63	0.016331	0.009576	L-ACg-WM, R-ACg-WM, L-VPR
43	62	0.018179	0.009104	R-UF, R-SLF
44	60	0.022558	0.016943	R-SLF
45	57	0.031291	0.036887	L-ST, L-Cerebellar WM, L- Thalamic WM
46	55	0.039005	0.007709	L-Cerebellar WM, R-SLF
47	55	0.039005	0.03198	R-SLF, L-Occipital WM
48	55	0.039005	0.012428	L-Occipital WM, R-EC

R – right, L- left; Key: MCP, Middle Cerebellar Peduncle; BCC, body of the corpus callosum; CST, corticospinal tract; ICP, inferior cerebellar peduncle; SCP, superior cerebellar peduncle; CP, cerebral peduncle; ALIC, anterior limb of the internal capsule; PLIC, posterior limb of the internal capsule; RLIC, retrolenticular limb of the internal capsule; ACR, anterior corona radiata; SCR, superior corona radiata; PCR, posterior corona radiata; PTR, posterior thalamic radiation; SS, sagittal striatum; EC, external capsule; CgC, superior cingulum; ST, stria terminalis; SLF, superior longitudinal fasciculus; UF, uncinate fasciculus; TAP, tapetum; DPF, dorsal prefrontal WM; VPF, ventral prefrontal white matter; DPCR, dorsal posterior corona radiata; MdLF, middle longitudinal fasciculus; PT, pyramidal tracts; OC, olivocerebellar; IFG-WM, inferior frontal gyrus WM; STG-WM, superior frontal gyrus WM; MTG-WM, middle temporal WM; MB-WM, midbrain WM; ACg-WM, anterior cingulum.

Table 2:

TBSS analysis: Main effects of maltreatment experience, sex, and social rank, and interaction effects (maltreatment by biological dam, maltreatment by rank).

Effect	Cluster	Size (voxels)	p-value	Average Beta from Fitted Model	White Matter Region
	1	66	0.011873	0.063313	R-EC, L-EC
Maltreatment Experience	2	56	0.034928	0.081644	L-PLIC, R-EC
	3	54	0.043577	0.058194	L-PLIC
Maltreatment Experience X Biological Dam	1	58	0.028044	0.043289	L-SLF
	2	56	0.034928	0.053197	L-SLF, L-MdLF
Maltreatment Experience X Rank	1	91	0.00097	−0.04625	R-IC
	1	81	0.002562	−0.035081	R-PLIC
Sex	2	56	0.034928	−0.034349	BCC, L-PLIC
	1	171	0.000001	0.026113	R-PLIC, R-RLIC
Rank	2	80	0.00283	0.024363	R-PLIC, L-PLIC, R-RLIC

R – right, L- left; Key: ALIC, anterior limb of the internal capsule; PLIC, posterior limb of the internal capsule; RLIC, retrolenticular limb of the internal capsule; EC, external capsule; IC, internal capsule.

Table 3:

TBSS analysis: Differences between animals raised by dams with similar patterns of maternal care as their biological dam (i.e. matched: control-control, maltreating-maltreating) versus those raised by dams with a different pattern of maternal care as compared to their biological dam (mismatched: maltreating-control, control-maltreating).

Cluster	Size (voxels)	p-value	Average Beta from Fitted Model	White Matter Region
1	58	0.028044	0.043289	L-SLF
2	56	0.034928	0.053197	L-MdLF

R – right, L- left; Key: SLF, superior longitudinal fasciculus; MdLF, middle longitudinal fasciculus.