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ORIGINAL ARTICLE

T1-Weighted/T2-Weighted Ratio Mapping at 5 Months Captures Individual Differences in Behavioral Development and Differentiates Infants at Familial Risk for Autism from Controls

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Abstract

Identifying structural measures that capture early brain development and are sensitive to individual differences in behavior is a priority in developmental neuroscience, with potential implications for our understanding of both typical and atypical populations. T1-weighted/T2-weighted (T1w/T2w) ratio mapping, which previously has been linked to myelination, represents an interesting candidate measure in this respect, as an accessible measure from standard magnetic resonance imaging (MRI) sequences. Yet, its value as an early infancy measure remains largely unexplored. Here, we compared T1w/T2w ratio in 5-month-old infants at familial risk (n = 27) for autism spectrum disorder (ASD) to those without elevated autism risk (n = 16). We found lower T1w/T2w ratio in infants at high risk for ASD within widely distributed regions, spanning both white and gray matter. In regions differing between groups, higher T1w/T2w ratio was robustly associated with higher age at scan (range: ~4–6.5 months), implying sensitivity to maturation at short developmental timescales. Further, higher T1w/T2w ratio within these regions was associated with higher scores on measures of concurrent developmental level. These findings suggest that T1w/T2w ratio is a developmentally sensitive measure that should be explored further in future studies of both typical and atypical infant populations.

Key words: biomarker, brain, early detection, infants, MRI, myelination, risk

Introduction

Identifying new ways of capturing structural brain development in early infancy is an important task for developmental neuroscience, which could inform our understanding of normative processes as well as individual differences (Almli et al. 2007; Knickmeyer et al. 2008). At the extreme, this variability may extend to atypical neurodevelopmental outcomes such as autism spectrum disorder (ASD), a heritable early onset condition defined by difficulties in social communication and interaction along with repetitive, restrictive behavior patterns, altered sensory processing and circumscribed interests (DSM-5 2013). Recent studies indicate hyper-expansion of the cortex in infants later diagnosed with ASD (Hazlett et al. 2011, 2017), as well as elevated levels of extra-axial cerebrospinal fluid (Shen et al. 2013, 2018).

Regarding white matter (WM), existing neuroimaging studies of ASD suggest atypical microstructural development, but the timing of onset, the nature, locality, level, and direction of this putative atypicality is still unclear (Courchesne et al. 2001; Cheng et al. 2010; Hazlett et al. 2011; Shukla et al. 2011; Weinstein et al. 2011; Walker et al. 2012). Animal models of ASD and postmortem analyses of the brains from individuals with ASD have revealed insufficient oligodendrocyte function and reduced myelination (Kennedy et al. 2016; Phan et al. 2020). Moreover, genes affecting oligodendrocyte function, proliferation of neural stem cells, and neuronal differentiation such as Tcf4, Olig2, and Sox2 have been linked to ASD (Parikshak et al. 2013; Moen et al. 2017). The involvement of genes affecting WM development and myelination motivates the assessment of these brain measures in relation to behavioral development in general, and in infants at risk for ASD in particular.

The earliest evidence of alterations of WM microstructure in ASD has been reported in a diffusion tensor imaging (DTI) study of infants at 6 months of age who later were diagnosed with ASD (Wolff et al., 2012). This longitudinal sibling study reported a higher WM integrity at 6 months, a lower rate of growth from 6 to 24 months, and a subsequent lower WM integrity by 24 months of age, in the subgroup who received an ASD diagnosis. These findings were useful first steps but the study did not include a normative reference group (not at risk for ASD), thus it is unclear how WM development underpins the maturation of social and nonsocial skills across the spectrum of infants with and without risk factors for ASD.

It has been suggested that the ratio of T1-weighted (T1w) and T2-weighted (T2w) signal intensities (T1w/T2w ratio) could represent an indirect measure of myelination (Glasser and van Essen 2011). Myelination is a core aspect of WM development that starts prenatally and unfolds rapidly in the first 2 years of life, and which has a critical role in supporting neural and behavioral functions. Myelination continues at a slower rate during childhood and adolescence until it plateaus in the third decade of life (Lebel et al. 2008; Dubois et al. 2014; Reynolds et al. 2019). Atypical maturation of WM microstructure has been linked to miscommunication between brain regions and to neurodevelopmental psychiatric conditions such as ASD (Weinstein et al. 2011; Wolff et al. 2012; Irimia et al. 2017; Bouziane et al. 2018; Dimond et al. 2019).

The intensity of T1w is positively and T2w is negatively associated with myelin-related contrast (Koenig 1991; Miot-Noirault et al. 1997). Thus, in principle, the T1w/T2w ratio enhances the sensitivity to myelin signal (Glasser and van Essen 2011). Calibration methods have also been developed for scaling the T1w and T2w intensities to adjust for differences across scanners and protocols, and make the across-subject comparisons more robust (Ganzetti et al. 2014).

Since T1w and T2w scans are the most common scanning sequences, T1w/T2w ratio mapping is an accessible approach, with no need for additional sequences or longer acquisition time (Hagiwara et al. 2018; Vandewouw et al. 2019). Although the correlation between T1w/T2w ratio and myelin water fraction has been reported to be poor in some studies (Arshad et al. 2017; Uddin et al. 2018, 2019), it has frequently been referred to as a proxy of myelin content (Shafee et al. 2015; Hagiwara et al. 2018). The technique has been related to myelination in both neonatal and pediatric brain imaging studies earlier (Lee et al. 2015; Soun et al. 2017; Vandewouw et al. 2019). Yet, to our knowledge, no study has investigated the potential of T1w/T2w ratio mapping to capture risk for neurodevelopmental conditions, or its ability to study individual differences in concurrent behavioral development in infancy.

Against this background, we assessed T1w/T2w ratio in 5-month-old infants to compare infants at high familial risk for ASD and those at low ASD risk. While this approach does not inform us about specificity with regards to ASD diagnoses, it can identify processes that are altered in infants at elevated risk for neurodevelopmental conditions. Nearly 50% of infants at high familial risk develop ASD or related neurodevelopmental problems like ADHD symptoms, motor atypicalities, language difficulties, etc. (Ozonoff et al. 2014). We also asked whether the T1w/T2w ratio was related to social and nonsocial behavior in the infants, and assessed its expectedly positive correlation with chronological age (Lee et al. 2015).

Materials and Methods

Participants

The sample was a magnetic resonance imaging (MRI) scanned subsample of the larger study, namely Early Autism Sweden (EASE), which follows infants from 5 months to 6 years of age using a comprehensive protocol (Falck-Ytter et al. 2018; Nyström et al. 2018, 2019; Thorup et al. 2018). In total, 46 five-month-old infants were successfully scanned during natural sleep at Astrid Lindgren Children's Karolinska University Hospital in Stockholm, Sweden. The EASE project is still ongoing, and the participating infants are not yet old enough for assessing ASD outcome status. Instead, the groups were stratified based on genetic risk for ASD. High-risk (HR) infants who had an older full sibling with clinical diagnosis of ASD (n = 29, f/m = 12/17) were recruited via the study's website, announcements and recruitments from clinical department. The diagnosis of the older sibling was confirmed through an interview with parents (by clinical psychologist) and inspection of obtained child psychiatric or pediatric records (more than 70% of all assessments included the ADOS (Lord et al. 2000) and/or the Autism Diagnostic Interview-Revised (ADI-R; Rutter, 2003)). As a normative reference, low risk (LR) infants (n = 17, f/m = 11/6) with no family history of ASD (recruited from via the Swedish population register) were also included. The study was approved by the Regional Ethical Board in Stockholm and conducted in accordance with the 1964 Declaration of Helsinki. The parents signed a written informed consent. Exclusion criteria were preterm birth (gestational age (GA) at birth <37 weeks) and confirmed or suspected medical problems, including visual/auditory impairment. In addition, requirements for MRI scanning had to be

fulfilled, such as absence of metallic implants in the child or the accompanying parent.

Behavioral Measures

Mullen Scales of Early Learning (MSEL) (Mullen 1995): The Mullen is a standardized measure of cognitive functioning for infants and preschool children from birth through 68 months, and was assessed by a trained experimenter. The Mullen assesses skills and abilities in five areas: gross motor, visual reception, fine motor, receptive language, and expressive language. This measure also yields a composite score, reflecting the overall developmental level. To assess the MSEL takes about 15 min for 5-month-old infants.

Vineland Adaptive Behavior Scales- II (VABS) (Sparrow et al. 2005): The VABS is a standardized parent interview consisting of 297 items providing a general assessment of personal and social functioning of individuals from birth to adulthood. Up to the age of 6 years, the VABS assesses adaptive behavior in each of four domains of functioning: communication, daily living skills, socialization, and motor. Given the young age of the infants, we focused on the subscales for Communication, Socialization, and Motor, since the Daily Living Skills domain at 5 months of age is of limited usability. The VABS usually takes about 10 to15 min to administer for parents with 5 months old infants.

Image Acquisition

Structural T1w and T2w scans were collected from the same scanning session from all participants during natural sleep using a 3 T Philips Ingenia scanner with an eight-channel coil. MRI scanning was scheduled to match the infant's sleep routine. Motion and head movement was limited using foam cushions. Neonate ear plugs and MRI-compatible noise-canceling headphones were also used to reduce the scanner noise. Parents were allowed to stay inside the scanner room if they preferred. An MRI-trained nurse performed the scanning and monitored the infants throughout the scanning sessions. In total, 73 infants were invited for scanning. Among those, 46 infants had successful scanning, 16 did not fall asleep, two were not scanned due to the parents' request, and the scanning was stopped for nine infants who woke up during scanning and did not fall asleep again immediately.

T1w images were obtained by a 3D Turbo Field Echo (TFE) sequence with TR = 8.199 ms, TE = 3.2 ms, field of view of 192 mm^2, matrix size of 192×192, and 160 slices with 1 mm slice thickness. T2w scans were acquired by a spin echo sequence, with TR = 7000 ms, TE = 300 ms, field of view of 192 mm^2, and 160 slices with 1 mm slice thickness. T1w and T2w scans were visually inspected for artifacts blind to the risk groups. Out of 46 scans, three were excluded due to poor quality of images. Thus, a total number of 43 infants (16 LR, f/m = 10/6, mean ± SD age at scan = 164.7 ± 15.7 days, mean ± SD GA at birth = 40.4 ± 1.6 weeks; and 27 HR, f/m = 12/15, mean ± SD age at scan = 157.4 ± 17.3 days, mean ± SD GA at birth = 39.4 ± 1.3 weeks) had both T1w and T2w scans and were included in the analysis.

Image Processing and Group Comparisons

Both T1w and T2w images for all infants were first used to construct age-specific multimodal templates using the Advanced Normalization Tools (ANTs) multivariate template construction tool (https://www.ncbi.nlm.nih.gov/pubmed/20851191). This method resulted in two templates (i.e., T1w and T2w templates) as well as the transformation matrices from individual images to templates. Sample slices of both T1w and T2w templates are shown in Figure 1a and b.

To compute the T1w/T2w ratio maps, the T2w images were first coregistered to the corresponding T1w images using antsRegistrationSyNQuick with six degrees of freedom. Next the T1w images and the coregistered T2w images were bias-corrected. The preprocessed images were then visually inspected blinded for group status, as a quality control. However, no preprocessed images were excluded due to poor data quality. To normalize the intensity histogram of the T1w and T2w images, we performed the external calibration method proposed by Ganzetti et al. (2014). To implement this, two masks covering the eyeballs and temporal muscles (shown in Fig. 1c) were selected on the T1w template and then transformed back to the individual space. The average intensities from these two masks were computed for all subjects. Using the formula proposed by Ganzetti et al. (2014) the intensity of T1w and T2w images were linearly scaled to calculate the calibrated T1w and T2w images. The calibrated T1w images were then divided by the calibrated T2w images to compute the T1w/T2w ratio maps.

In order to run a voxel-wise analysis to compare the T1w/T2w ratio maps of LR and HR groups, the T1w/T2w ratio maps were transformed to our age-specific T1w template using the same transformations matrices for all T1w images. The images were then smoothed by a 3 mm Gaussian kernel and fed into the FSL-Randomise tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise, (Winkler et al. 2014)). Age at scan and sex were included as covariates in the group comparisons. FSL-Randomise was performed with 10 000 permutations and the results were corrected with the family-wise error (FWE <0.01) using the threshold-free cluster enhancement (TFCE) method (Smith and Nichols 2009).

To anatomically localize the significant regions, the Montreal Neurological Institute (MNI)-T1w-template was nonlinearly transformed to our age-specific T1w template. The same transformation matrix was used to map the Johns Hopkins University (JHU) white-matter tractography atlas as well as the Harvard-Oxford cortical atlas to our age-specific template. The significant regions were then labeled according to their overlaps with atlas labels (Supplementary Table). Note that due to the use of adult brain atlas, the anatomical localization at this early age is not precise and these results need to be interpreted with caution.

Statistical Approach for Brain-Behavior Associations

The T1w/T2w ratio measure averaged across voxels showing differences between LR and HR group (Fig. 2a) was first tested for associations with age at scan. Next, we tested for associations with the VABS and MSEL behavioral scales, using a hierarchical linear regression, with age at scan and sex entered in the first step and the behavioral scales entered in the second. To follow up this initial overall model, we used partial correlation (correcting for age at scan and sex) on the individual scales. Finally, we checked the possible moderating effect of group in any significant correlations using a univariate general linear model. Here, the behavior measure was the dependent variable, while group, sex, age at scan, T1w/T2w ratio, and the group* T1w/T2w ratio interaction were entered in the model as independent model terms.

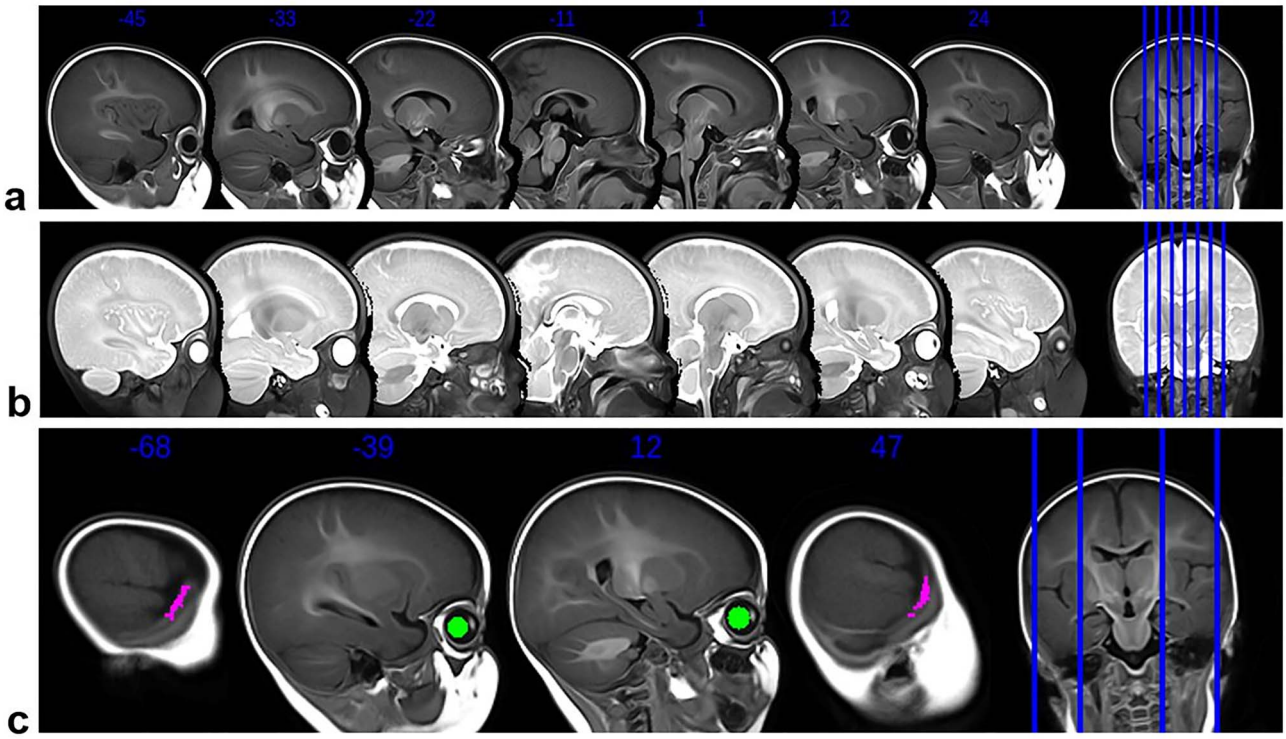

Figure 1. The age-specific templates used in this study. (a) T1w template, (b) T2w template. (c) the eyeball and temporal masks (shown by green and purple, respectively) overlaid on the age-specific T1w template.

Results

Voxel-wise analysis of the T1w/T2w ratio maps (corrected for age at scan and sex) showed widespread significant differences between the LR and HR infants, with the LR group consistently having higher T1w/T2w ratio than the HR group (Fig. 2a). Figure 2b, c illustrates the main WM and GM regions associated with these differences (see Methods and Supplementary Table).

In the total sample, the T1w/T2w ratio (averaged across the voxels which showed significant group differences; Fig. 2a) was positively associated with age at scan (Pearson $r = 0.40$, $P = 0.008$; Fig. 3), but was not associated with GA at birth ($r = 0.13$, $P > 0.25$; GA was not available for five subjects, hence $n = 38$). For these two correlations, we did not control for sex as it was equally distributed within the total sample and T1w/T2w ratio did not differ between female and male infants (f/m = 22/21, $P > 0.25$).

Next, we evaluated the potential effect of group in the above associations using a univariate general linear model with T1w/T2w as the dependent variable, group as fixed factor and age and sex as covariates. We found that group and age at scan were significant (group: $F(1,42) = 5.20$, $P = 0.03$; age: $F(1,42) = 4.54$, $P = 0.04$), while sex did not reveal significant effect ($P = 0.09$; we also checked whether the group × age interaction was significant; it was not ($P > 0.25$)).

The behavioral measures at 5 months of age including MSEL early learning composite score (experimenter-rated) as well as parent-rated VABS communication, VABS socialization, and VABS motor skills did not differ significantly between LR and HR groups (all $P \geq 0.10$; Table 1).

To investigate brain-behavior associations, we performed a hierarchical linear regression with the average T1w/T2w ratio from voxels with significant group differences (Fig. 2a) as the dependent variable, age at scan and sex entered as predictors in step 1 and all (MSEL and VABS) behavioral scales entered at step 2. There was a significant increase in model fit from model 1 to model 2 (F change $(4,33) = 3.344$, $P = 0.021$, Model 1 adjusted $R^2 = 0.123$, Model 2 adjusted $R^2 = 0.300$). Model fit changed significantly also when also including risk group in Step 1 ($P = 0.043$). Further, the increase in model fit was significant also when entering either MSEL and the VABS scales separately in step 2. In neither of these models, there were any specific scales with significant unique contribution (except in the model with only MSEL, i.e., just one added predictor). This suggests that the behavioral scales collectively capture variability in T1w/T2w ratio that goes beyond that captured by sex and age, but that most of this additional variance is shared between multiple predictors. Indeed, zero order correlations between the behavioural predictors were all significant (Pearson correlations range: 0.350–0.611) with the exception of VABS socialization and VABS communication which did not reach statistical significance ($r = 0.297$, $P = 0.06$). Figure 4 shows the correlations between the T1w/T2w ratio and the four predictors entered in Step 2 in the above model.

Discussion

This study suggests that the T1w/T2w ratio at 5 months of age is lower in infants at familial risk for ASD compared with LR control infants, and that it relates to individual differences in concurrent behavioral development. Further supporting its developmental significance, we observed a robust association with age at scan, even within the limited age range covered by the study. It is in line with previous study assessing the

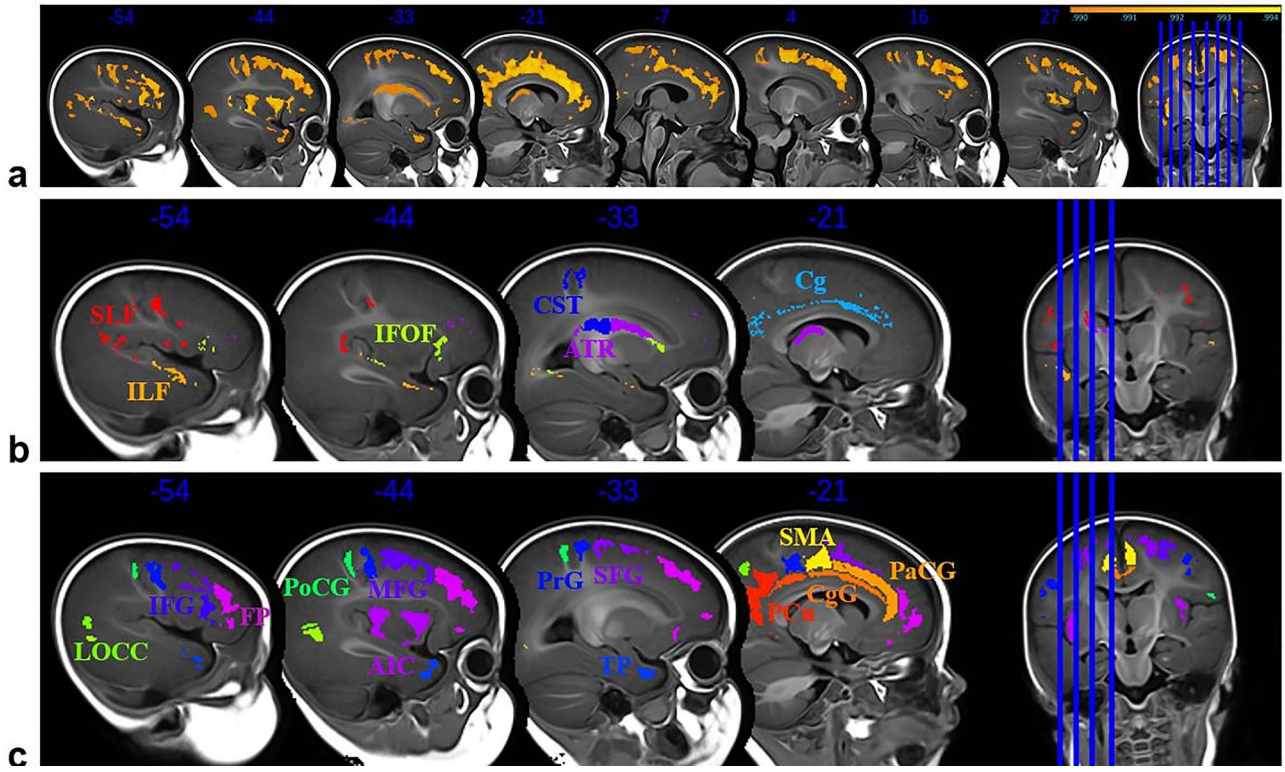

Figure 2. Results for group comparison. (a) Significant differences of T1w/T2w ratio between the low-risk and high-risk groups (LR > HR, *P* value corrected at FWE <0.01). (b) The white matter (WM) regions were superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior occipito-frontal fasciculus (IFOF), anterior thalamic radiation (ATR), corticospinal tract (CST), and cingulum (Cg). (c) The gray matter (GM) regions were frontal pole (FP), superior frontal gyrus (SFG), inferior frontal gyrus (IFG), middle frontal gyrus (MFG), supplementary motor area (SMA), insular cortex (AIC), precentral gyrus (PrG), postcentral gyrus (PoCG), cingulate gyrus (CgG), paracingulate gyrus (PaCG), precuneus (PCu), temporal pole (TP), and lateral occipital cortex (LOCC).

Table 1 Descriptive statistics of the behavioral measures. The n for each measure varies slightly as a function of availability of each measure

behavioral measures	Group (n)	Min	Max	Mean	SD	SE	t (df = 41)	*P* value
MSEL early learning	LR (16)	89	112	101.06	8.04	2.01	1.70	.10
composite score	HR (27)	74	120	95.48	13.46	2.59		
VABS	LR (16)	22	35	29.88	4.02	1.00	.30	.76
communication	HR (26)	22	42	29.46	4.46	.87		
VABS socialization	LR (16)	23	33	30.00	2.71	.68	.18	.86
	HR (25)	17	36	29.80	3.92	.78		
VABS motor skills	LR (16)	25	34	28.19	2.66	.67	.79	.43
	HR (24)	15	33	27.33	3.69	.75		

link between T1w/T2w measures and age in neonates aged 1–8 weeks (Lee et al. 2015). Follow-up analyses of the current cohort will help clarifying if T1w/T2w ratio at 5 months predicts long-term variability in social and nonsocial behavior.

As mentioned in the introduction, studies of the neonatal brain (Lee et al. 2015; Soun et al. 2017) and histological analyses of patients with multiple sclerosis (Nakamura et al. 2017; Righart et al. 2017) suggest that the T1w/T2w ratio is an indirect measure of myelination. However, the specific link between T1w/T2w ratio and actual myelin content has been doubted by others (Uddin et al. 2018, 2019) due to its poor correlation with myelin water fraction (MacKay and Laule 2016). While the link to myelination remains undetermined at this point, our results suggest that T1w/T2w ratio captures brain processes that are associated with chronological age as well as with indices of social and nonsocial development at this early age.

Previous studies have indicated a positive correlation between myelination in infancy and later cognitive abilities as well as concurrent links later in childhood in typical development using other MRI techniques such as DTI and myelin water fraction (Short et al. 2013; O'Muircheartaigh et al. 2014; Deoni et al. 2016; Dai et al. 2019). Although these MRI techniques are highly informative, additional MRI sequences and longer scanning time are required during scanning sessions to provide the relevant microstructural properties. In contrast, T1w and T2w are usually available in almost all MRI studies. Due to the accessibility, the current MRI results can be easily replicated in other studies of infants.

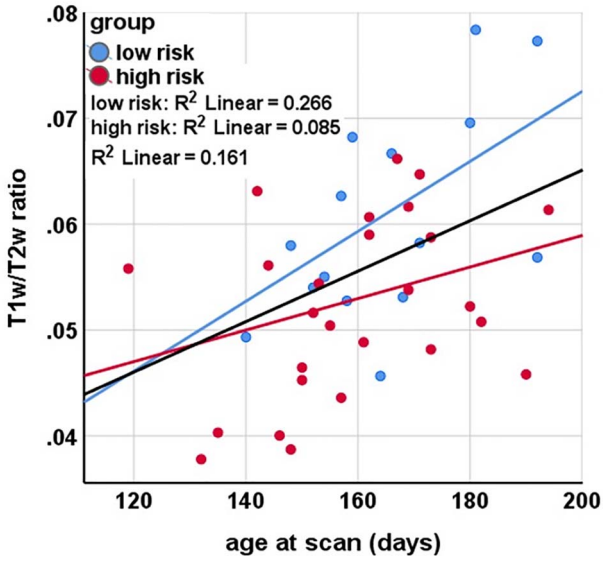

Figure 3. Scatterplots for the correlations between the T1w/T2w ratio (averaged across voxels showing significant differences between the low-risk and high-risk infants; Fig. 2a) and age at scan. The black line shows the linear regression line across all subjects together, while the blue and red lines illustrate the regressions for low-risk and high-risk groups, respectively. R^2 of the combined data and the group-split data are shown in the figure. Groups (low risk vs high risk) are plotted separately for descriptive reasons only; the group × age interaction was not significant.

Some earlier studies have used DTI to examine WM microstructural differences in ASD compared with controls (Lebel et al. 2008; Travers et al. 2012; Walker et al. 2012; Wolff et al. 2012). Most relevant in the current context, one study found initial higher WM integrity followed by a slower rate of growth from 6 to 24 months in infants later diagnosed with ASD (Wolff et al. 2012). Similar to T1w/T2w ratio mapping that is not specific to myelin content (Uddin et al. 2018, 2019), DTI measures may reflect many other microstructural components of WM, such as fiber orientation, neural packing, axonal size, and density (Laule et al. 2007; Mädler et al. 2008). Thus, the specific contribution of differences in myelination to the results is difficult to establish with either T1w/T2w ratio or DTI. Notably, while the Wolff et al. study compared infants at risk for ASD who either developed or did not develop ASD at follow-up (no LR group was included), the current study compared infants at risk for ASD with LR controls.

Although the anatomical labeling of specific regions (Fig. 2b,c and Supplementary Table) needs to be interpreted with caution given the difficulty of precise anatomical localization at this early age, it is notable that it implicated several regions that have been previously found altered in autistic individuals compared with neurotypical controls (Duerden et al. 2012; Haigh et al. 2020). For example, ATR, SLF, ILF, and the cingulum together with their adjacent cortical areas have shown to be involved in socio-communicative and emotional behavior (Cheon et al. 2011; Nair et al. 2013; Parkinson and Wheatley 2014; Im et al. 2018).

While the current study suggests that T1w/T2w ratio mapping is a promising method for this age that can be used in future studies, the current study has several limitations that should be kept in mind. First, the small sample size entails that we had low statistical power. Another limitation is the unbalanced sex ratio across the two groups. While we statistically controlled for this, this cannot entirely rule out sex as a confounder in the analysis. Moreover, although we did not reveal any significant effect of sex in the current study, sexual dimorphisms are present structurally and functionally in human brain before birth (Wheelock et al. 2019) and throughout the lifespan (Gilmore et al. 2007; Koolschijn and Crone 2013; Satterthwaite et al. 2015). As some brain areas found in the present work have previously been found to differ between males and females (e.g., the frontal and occipital regions) (Knickmeyer et al. 2014; Ruigrok et al. 2014; Wheelock et al. 2019), future studies may have this potential issue in mind. A further limitation of the study is the volume-based registration approach for aligning the individual brains to the template, and the use of adult brain atlases for the anatomical labeling. As noted above, this rather coarse approach entails that division into GM vs WM and the specific localizations need to be interpreted with caution. Further, the approach entails that several aspects of brain development, including cortical thickness and surface area could contribute to the observed differences and associations. Future studies could benefit from registration based on cortical segmented areas for GM and tract-based approach for WM (as proposed by Vandewouw et al. 2019). Future studies should also compare T1w/T2w ratio with other measures, in this age range and in relation with risk for ASD, to fully understand the tissue characteristics deriving the difference between the typical and atypical populations. Finally, the current analysis did not correct for motion artifacts. While the infants were physically stabilized during scanning (see Methods), movement may still occur and we acknowledge that this is a limitation that ideally should be addressed in follow-up analyses.

For the brain-behavior associations, it is important to keep in mind that the overall regression analysis did not indicate that there were unique contributions by the separate behavioral scales to the brain measure. Thus, from a statistical point of view, the different behavioral scales share variance that is associated with the brain measure, beyond the variance explained by age and sex.

It is also important to emphasize that given the lack of outcome data, we cannot know if the observed early differences predict a later ASD diagnosis. That said, ASD is a heterogeneous condition and 50% of infants with a sibling with ASD will go on to experience a range of neurodevelopmental difficulties which do not necessarily reach the threshold for a clinical diagnosis of ASD (Ozonoff et al. 2014). Moreover, we now know that parent environment can alter the outcomes of infants at risk of ASD (Green et al. 2017), and that secondary and/or compensatory mechanisms influence whether a diagnostic threshold is passed (Happé and Ronald 2008). Thus, it is unlikely that there is an inflexible relationship between the 5-months-old brain and a later diagnosis.

Conclusions

In summary, this study is the first to use T1w/T2w ratio mapping in infants at risk for ASD. The results suggest that at five months of age, infants at risk for ASD have lower T1w/T2w ratio than control infants. Further, we found that T1w/T2w ratio in the areas differing between groups tracked chronological age at short timescales in infancy, and was associated with individual differences in social and nonsocial behavioral development. Together, these results motivate further investigation of the T1w/T2w ratio as a promising measure of early brain development, in typical as well as atypically samples.

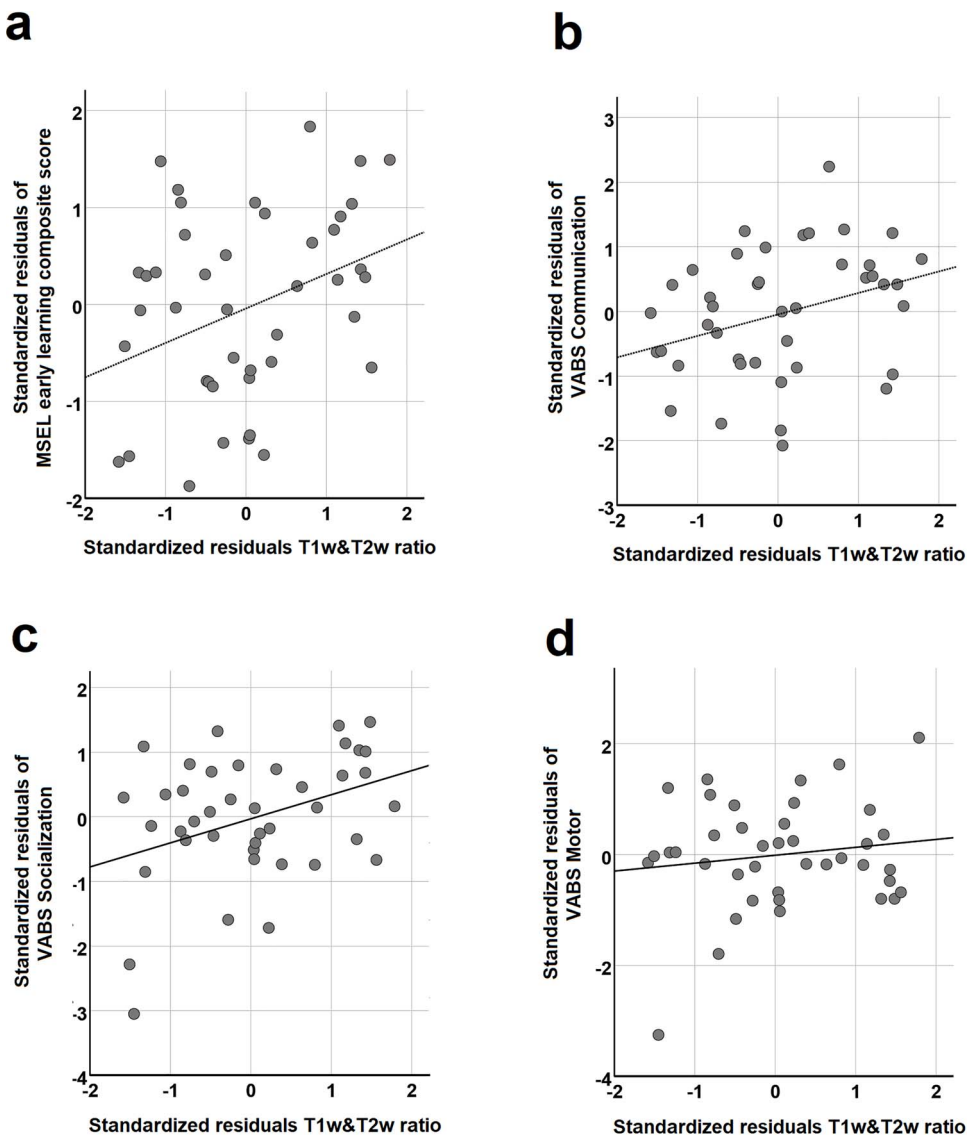

Figure 4. Whole sample scatterplots of the partial correlations between the average T1w/T2w ratio for voxels that differed between HR and LR groups (shown in Fig. 2a) and (a) the MSEL early learning composite score ($r = 0.320$) and (b) the VABS communication scores ($r = 0.301$), (c) the VABS socialization scores ($r = 0.354$), and (d) the VABS motor scores ($r = 0.144$). In keeping with the overall model (text), these correlations are corrected for the effect of age at scan and sex. We found no evidence that any of these associations were significantly moderated by risk group (all $P > 0.05$; corrected for four tests).

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Notes

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