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Neuroanatomical Correlates of Emotion-Processing in Children with Unilateral Brain Lesion: A Preliminary Study of Limbic System Organization

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Abstract

In this study, MRI and DTI were employed to examine subcortical volume and microstructural properties (FA, MD) of the limbic network, and their relationships with affect discrimination in 13 FL (6 right FL, *M* = 10.17 years; 7 left FL; *M*=10.09 years) and 13 typically-developing children (TD; *M*= 10.16 years). Subcortical volume of the amygdala, hippocampus and thalamus and FA and MD of the fornix and anterior thalamic radiation (ATR) were examined. Results revealed no group differences across emotion-perception tasks or amygdalar volume. However, contrasting neuroanatomical patterns were observed in right versus left FL youth. Right FL participants showed increased left hippocampal and thalamic volume relative to left FL participants; whereas, the latter group showed increased right thalamic volume. DTI findings also indicated right FL children show greater MD of right fornix than other groups, whereas, left FL youth showed greater MD of left fornix. Right FL youth also showed lower FA of right fornix than left FL children, whereby the latter showed greater FA of left fornix and ATR. Differential associations between DTI indices and auditory/visual emotion-perception were observed across FL groups. Findings indicate diverging brain-behavioral relationships for emotion-perception among right and left FL children.

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Keywords

focal lesion; emotion perception; DTI; anterior thalamic radiation; fornix; limbic system

Introduction

In general, early neural insult in humans has been shown to yield more positive cognitive and behavioral outcomes than later brain damage to the same regions (Bates et al, 2001; Ballantyne et al., 2008; Reilly et al., 2008; Stiles et al., 2012), although the severity of the injury highly affects the degree of functional recovery (Anderson et al., 2005; Anderson, Spencer-Smith, & Wood, 2012). Early childhood experiences have been postulated to have prominent effects on brain development, as formation of certain circuits and functions such as vision are arguably experience-dependent (Greenough, Black & Wallace, 1987). However, despite the vulnerability of brain development to early experiences, the brain also exhibits a remarkable ability to adapt and reorganize following neural insult during this period, a phenomenon coined as neural plasticity (Stiles et al., 2012). Importantly, investigations of children with perinatal stroke have allowed neuroscientists to fully appreciate and examine the extent and limitations of brain plasticity across developmental stages. In a similar vein, investigations with children with focal lesions (FL; i.e., localized brain injury) have provided evidence that recovery from neural insult varies as a function of cognitive or behavioral domain (Murias, Brooks, Kirton, & Iaria, 2014; Stiles et al., 2012). Hemispheric location of the FL has been associated with differential recovery of skills, including visuospatial processing (Akshoomoff et al., 2002; Stiles et al., 2003, 2003; Yousefian, Ballantyne, Doo, & Trauner, 2015), use of affective language and emotional expression (Lai & Reilly, 2015), functional language (Stiles et al., 2012), and processing of affective prosody (Trauner et al., 1996). Despite the growing research on children with FL, the neurobehavioral plasticity of emotion processing remains an understudied area. Towards this end, the present study aimed to examine morphological and tissue property measures of the brain structures and circuits associated with affect-processing in children with FL, and their association with their emotion-perceptual abilities.

The ability to recognize emotional cues is fundamental in social interactions, as these signals are necessary in the decoding of others' mental state and behavioral responses. In infancy, emotion perception gradually becomes more organized. By the first eight months, infants can broadly discriminate between positive versus negative-valenced faces (e.g., fearful, angry; for a review see Grossman, 2013). By five months, infants demonstrate the ability to discriminate happy, sad, and angry vocal expressions (Walker-Andrews & Lennons, 1991). As children become more adept in distinguishing affective expressions, their emotion comprehension also expands to include more complex emotions, which may be contingent on social mores (e.g., shame, embarrassment). Emotion perception of social stimuli such as faces and human vocalizations has been suggested to mature earlier than perception of non-social content, as the former may be adaptive for young children to use affective signals to learn from others (e.g., social referencing to adults; Klinnert, Campos, Sorce, Emde, & Svejda, 1983).

Although basic emotion-perception skills emerge in early infancy, the development of affect-processing faculties is highly sensitive to both positive early experiences and adversities (Joseph, 1999), and continues to mature well into adolescence (Casey, Jones, & Hare, 2008). The limbic system, which includes subcortical structures such as fusiform gyrus, thalamus, amygdala, and hippocampus, is a network of substrates dedicated to processing and experiencing emotions (Gur, Schroeder, Turner, McGrath, et al., 2002; Hariri, Bookheimer, & Mazziotta, 2000; Phan, Wager, Taylor, & Liberzon, 2002). This network of circuits is sensitive to social environmental input including parent-child interactions, and reportedly modifies in face of enriched interactions or privation (Davidson, Jackson, & Kalin, 2000; Braun & Bock, 2011). However, the degree to which this network is malleable and capable of reorganization after early neural insult remains unclear. Notably, investigating emotion-perceptual development in the context of early brain damage will be informative in building targeted interventions and add to the current literature regarding neural plasticity.

To date, research on emotion-processing skills among children with FL is limited. Notably, adults and children with stroke both show abnormalities in structure and function in the limbic region (i.e., hippocampus, amygdala, thalamus) regardless of whether the insult was localized to the frontal area (Beauchamp et al., 2011; Gold & Trauner, 2014; Keightley et al., 2014), which in turn may account for emotion-perceptual deficits in these individuals. Beauchamp and colleagues (2011) found that children who experienced a brain injury in childhood show smaller hippocampal volume and increased amygdala volume up to 10 years post-insult, suggesting that there may be pathophysiological changes in subcortical regions despite the brain injury occurring elsewhere. Thus far, empirical evidence indicates that children with right focal lesion (RFL) show more difficulty discriminating facial affective expressions and affective prosody (for a review see Stiles, Reilly, Paul, & Moses, 2005). Similarly, studies of adults with stroke have shown that the right hemisphere has a central role in emotion-processing (Adolphs et al., 2000; Borod et al., 1992; 2000; 2002), leading to the hypothesis that right hemisphere is dominant for affective perception (Borod et al., 2002). However, emerging evidence has shed light that left subcortical structures such as the amygdala may have important influences on auditory emotion perception indirectly through auditory cortex (Frühholz et al., 2015). Taken together, pathological changes in the emotion-processing center of the brain, i.e., limbic system, may occur following perinatal stroke; yet, the extent to which the brain adapts and reorganizes to preserve emotion perceptual functions is unknown.

The current exploratory study aimed to elucidate emotion development in children with FL versus their typically developing (TD) age and gender-matched peers by examining the anatomical structure and fiber integrity of the limbic system and its association with their emotion-perceptual functioning. First, magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) was used to investigate differences in cortical volume of the limbic structures (i.e., hippocampus, thalamus, and amygdala) and fiber integrity of the fornix (i.e., circuit that bridges the hippocampus and hypothalamus) and anterior thalamic radiation (ATR; i.e., fibers connecting thalamus to frontal region). Second, emotion-perception of social and non-social visual and auditory stimuli was compared in FL children versus TD counterparts. Third, to explore neurodevelopmental differences linked to affect processing in children with right versus left FL (LFL), associations between cortical volume and fiber

integrity of the noted subcortical substrates with the visual and auditory emotion-perception performance were examined. Based on aforementioned investigations comparing FL versus TD children and adults, we generally anticipated FL children to show reduced volume in limbic substrates, ipsilateral to the lesion, and reduced fractional anisotropy (FA) of limbic circuits, a common neural marker of neurodegeneration or underdevelopment (Bennett et al., 2010). However, given the paucity of research, no a priori predictions between left versus right FL children were made across behavioral and brain measures.

Methods

Participants

A total of 26 children participated in this study. Of these, thirteen comprised of children with focal lesion (FL) and thirteen typically developing (TD) counterparts matched on gender and age, $t(24)=0.04$. Table 1 outlines demographic information of the participating children. All participants were recruited through University of California, San Diego (UCSD) as part of a multi-project program. Our collaborative research team screened participants based on the following measures: normal or corrected vision/hearing, English native-language speaker, and no remarkable mental health history. TD participants were also screened for history of neurological trauma and none had a history of chronic medication use. Caregivers completed an interview and extensive demographic and family history questionnaires to assess whether participants met the aforementioned criteria. To be included in the FL group, children must have met these following inclusionary criteria: single, unilateral brain lesions that were the result of a perinatal stroke documented by a Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scan. These individuals do not have a history of a condition that might have caused more global brain damage (e.g., bacterial meningitis, encephalitis, or severe closed head trauma). The TD comparison group also completed MRI scans to ensure no significant neurological abnormalities. Table 2 outlines the lesion information per FL participant, all confirmed with imaging scans. Caregivers and child participants provided consent and assent for participation, respectively. Study protocols were approved by the Institutional Review Boards at the Salk Institute and UCSD.

Participants completed the Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporations, 1999) to determine their overall intellectual functioning and both verbal and non-verbal abilities. Table 1 shows that TD participants scored higher than FL children on full intelligence quotient (FIQ), $t(24)=4.16$, $p<0.001$; verbal IQ (VIQ), $t(24)=4.02$, $p<0.001$; and performance IQ (PIQ); $t(24)=3.41$, $p=0.002$.

Stimuli

Auditory—Social and non-social stimuli were presented. For the social stimuli, auditory clips of non-linguistic vocal sounds from the “Montreal Affective Voices” (standardized stimuli available at http://vnl.psy.gla.ac.uk/info.php?file=mav) were presented. The duration of the vocalized expression lasted approximately 1353 ± 642 ms. A total of 24 social clips were used, and 8 were of three different affective states (happy, fearful, sad). The non-social condition comprised of 24 auditory clips of musical pieces, normed and created by Marsha Bauman of Stanford University for studies to investigation musicality among individuals

with neurodevelopmental disorders. Analogous to the social condition, of the musical pieces, eight auditory clips evoked each of the three emotions (fearful, happy, sad) and lasted same duration (1354.67 ± 538.93 ms). These stimuli have been used to examine social vs. non-social processing of affect among individuals with neurodevelopmental disorders (Järvinen et al., 2012; Järvinen et al., 2015; Järvinen-Pasley et al., 2010b).

Visual—The visual emotion discrimination experiment included 24 social and 24 non-social stimuli, eliciting the three emotions (fearful, happy, sad). For the social condition, facial images from the NimStim Face Stimulus Set (Tottenham et al., 2009) were employed. Non-social stimuli comprised of 24 scenic stimuli from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008). None of the IAPS images employed in this study contained human faces. Detailed description of the visual stimuli has been is outlined in Järvinen et al. (2012).

Procedures

Auditory Affect-Discrimination—Experimental methods for this task are found in Järvinen et al., 2015. Both visual and auditory discrimination tasks were administered through PsyScope software (Cohen, MacWhinney, Flatt, & Provost, 1993) on a laptop. Participants were presented a fixation stimulus (i.e., a smiling animated face) for 1000 ms on a laptop screen to center participants' attention. Participants were also told that this stimulus signifies that target stimuli will be presented shortly. Auditory stimuli were heard through a noise-reducing headphone at approximately 75db SPL. Two stimuli pairs that are both social or non-social were presented consecutively. Subsequently, participants were asked, "was the emotion the same or different in the two sounds?" and shown a response screen with "SAME" and "DIFFERENT". Participants were told to give a verbal response, so that the experimenter sitting behind him or her could enter their response on the keyboard. A total of 48 trials were presented and half of these trials had pairs with the same emotional valence while the others were incongruent. While the stimulus pairs were fixed, the trials were pseudo-randomized.

Visual Affect-Discrimination—The visual discrimination task was similar to the auditory task above and administered through the same software. A fixation cross was displayed for 500 ms to warn participants of subsequent target stimuli, each of which was shown for 3000 ms. After, two visual stimuli of the same domain (social, non-social) were shown side by side. Participants were asked to match the emotion shown by the target to the emotion conveyed by one of the two pictures. Children were asked to either point to the picture they believed matched the emotion of the target stimulus, or verbally indicate "1" or "2". The same response recording procedure was applied in both the auditory and visual tasks. Although the target and subsequent pairs were fixed, the trials were randomly selected. A total of 48 trials were administered with half of these with the correct response on the right side and the other half on the left. Paired t-tests suggested no specific preference to the location of the accurate response.

MRI data acquisition—A 1.5 Tesla GE Signa HDx 0M5 TwinSpeed scanner was used to obtain MRI scans (GE Healthcare, Wukesha, WI) (TE = 3.0 msec, TR = 8.7 msec, TI = 270

msec, flip angle = 8°, delay = 750 msec, bandwidth = ± 15.63 kHz, field of view = 24 cm, matrix = 192 × 192, voxel size = 1.25 × 1.25 × 1.2 mm). Real-time, prospective motion tracking and correction (PROMO) was employed to correct for motion artifacts (Brown et al., 2010). Information regarding the spiral navigator pulse sequences and an extended Kalman filter algorithm applied in this study is found in White et al., (2010). AtlasTrack automated DTI was used to produce the white matter streamlines (see Hagler et al., 2009). The methods implemented to process the MRI data are described in detail in Brown et al. (2012), and Mills et al. (2013a; 2013b).

Data Analysis

Across auditory and visual discrimination tasks, participants' responses were coded for accuracy (1=correct, 0=incorrect). Subsequently, accuracy across tasks was computed by dividing the number of correct trials out of the total trials administered. Based on current imaging scans and medical records, the presence of a subcortical lesion was coded to use as a covariate. For behavioral data, repeated measures analysis of variance (ANOVA) were employed with Group (TD, LFL, RFL) as the between-groups factor; Social (social, non-social) and Emotion (fearful, happy, angry) as within-subject factors, percent of trials correct as a dependent variable, and FIQ and presence of subcortical lesion as covariates. For the MRI and DTI data, analysis of covariance (ANCOVA) was applied to determine group differences in subcortical volume of limbic substrates (thalamus, amygdala, hippocampus), and both FA and MD of limbic-frontal pathways. Specifically, fibers of the fornix and anterior thalamic radiation (ATR) were examined with group as a fixed between-group factor, and FIQ, presence of subcortical lesion, and total subcortical volume or fibers were covariates. Bonferroni post-hoc tests were computed to assess pairwise differences. Based on the results from ANCOVAs, Pearson correlations were conducted to examine associations between anatomical and fiber integrity of limbic network to auditory and visual emotion perception in RFL, LFL and TD participants.

Results

Behavioral, MRI, and DTI Analysis

Comparisons Across FL and TD participants—No significant group differences were observed between the three groups on the visual or auditory affect-discrimination experiments, $Fs<0.66$, *ns*. FIQ was the only significant covariate for visual discrimination data, $F(1,16)=7.81$, $p=0.01$, $\eta^2=0.32$. No interactions involving the group variable reached significance.

Table 3 lists the descriptive statistics of the subcortical volumes across groups. Significant group differences were observed in subcortical volumes of the right and left thalamus, $Fs>9.68$, $ps = 0.001$, $\eta^2_{right}=0.49$, $\eta^2_{left}=0.40$; and left hippocampus, $F(2,20)=4.18$, $p=0.03$, $\eta^2=0.30$. No group effect was observed for bilateral amygdalar volume, $Fs<3.28$, *ns.* Bonferroni post-hoc tests indicated RFL children had greater volume in the left thalamus than the LFL; whereas, LFL participants had greater volume of the right thalamus, $ps=0.002$. Additionally, the RFL group showed greater left hippocampal volume than the LFL group, $p=0.028$.

Table 4 outlines the average MD and FA of fornix and ATR as a function of group status. Group differences were observed solely for MD of the right and left fornix, *F*s>4.17, *p*s<0.035, η^2_{right}=0.44, η^2_{left}=0.30; but not ATR, *F*s<1.44, *ns*. Post-hoc tests showed RFL children had higher MD of right fornix than both TD and LFL participants, *p*s<0.04; whereas, the LFL group showed higher MD within the left fornix than RFL peers, *p*=0.03. Significant group differences were observed in FA of right and left fornix, *F*s>5.53, *p*s<0.015, η^2_{right}=0.36, η^2_{left}=0.45; and left ATR, *F*(2,24)=5.78, *p*=0.01, η^2=0.37, although pairwise comparisons showed contrasting directions. RFL children showed lower FA of the right fornix than LFL, *p*=0.02. LFL children displayed decreased FA of the left fornix and ATR as compared to both RFL and TD groups, *p*s<0.045. In brief, although no behavioral differences were observed between children with FL and TD, the hemispheric location of the lesion was associated with altered white matter tissue properties within the limbic network circuitry.

Qualitative comparisons between two FL participants with remaining FL and TD groups—One participant with RFL and one with LFL scored over two standard deviations below the average performance of the remaining FL groups and TD participants on the visual and auditory discrimination task, respectively (see Table 5). The behavioral data were reanalyzed without the outliers; however, similarly, no significant group effects were observed across auditory or visual discrimination tasks. Instead, the differences between clinical groups diminished with the removal of these data. Subsequently, ANCOVA were computed again with the remaining RFL, LFL, and TD groups, with the noted participants' data removed. In brief, similar outcomes as noted above were found with the exception of a weaker group effect observed for MD of the left fornix, *F*(2,17)=3.17, *p* = 0.06. Additionally, the group effect observed for FA of the right fornix dissipated.

The noted outlying participants' data were qualitatively compared to the remaining RFL and LFL participants as well as the TD group across MRI and DTI measures. Differences in obtained scores characterized by two standard deviations or greater are highlighted in this sections. As outlined in Table 5, the RFL participant with outlying behavioral data had significantly reduced subcortical volume across bilateral hippocampus, right amygdala, and left thalamus relative to both the remaining RFL participants, and less volume in the right hippocampus and right thalamus compared to the TD group. In effect, this participant also showed increased MD and reduced FA of bilateral fornix and ATR relative to both the remaining RFL and TD participants. Altogether, this right FL participant showed weaker fiber integrity and anatomical structure of limbic structures, which likely contribute to poorer emotion perception across sensory modalities.

In contrast, the left FL participant who performed over two standard deviations below respective FL group and TD comparison participants on auditory discrimination task showed reduced subcortical volume specific to the left hippocampus and thalamus relative to TD comparison group, and similarly, less volume in the thalamus compared to the remaining LFL participants. This participant also showed more lateralized weakening of fiber integrity. Specifically, the participant yielded reduced MD and increased FA of left fornix and left ATR relative to LFL and TD group, suggesting damage localized to left hemisphere may contribute to a distinct weakness in emotion discrimination of the auditory domain.

Associations between cortical volume, MD, and FA of limbic substrates with emotion perception

Analyses revealed contrasting associations between total accuracy in visual and auditory affect-discrimination tasks and subcortical volumes of limbic substrates across TD and FL groups. Among the TD children, greater right and left hippocampal and thalamic volumes were associated with lower auditory emotion-discrimination, $rs<-0.68$, $ps<0.03$. In contrast, among LFL participants, greater left thalamic volumes were correlated with more accurate discrimination of auditory affective stimuli, $r(5)=0.97$, $p=0.006$. No associations were observed among RFL children.

Table 6 outlines the correlations between MD and FA of fornix and ATR with visual and auditory emotion-perception across FL groups. Among the RFL group, higher FA of the right fornix and of the ATR (left and right) was associated with stronger visual and auditory emotion-discrimination abilities respectively, $ps<0.035$. Additionally, increased FA of the left fornix was associated with better performance on the auditory emotion-perceptual task, $p=0.02$, and reduced MD of the right fornix was related to more accurate emotion discrimination of visual stimuli, $p=0.005$. In contrast, among the LFL group, greater FA of left fornix and left ATR, and lower MD of the left fornix and left ATR were associated with better auditory emotion-discrimination, $ps<0.05$. Further, greater MD of the right fornix was correlated with stronger emotion-perceptual skills for visual stimuli, $p=0.02$. Altogether, among FL children, increased FA of the subcortical circuits ipsilateral to lesion was linked to stronger emotion discrimination performance, whereas, reduced MD on the same side of lesion was associated with greater emotion-perceptual deficits. Notably, these associations were generally observed within the emotion perception of visual stimuli for RFL group, whereas they were found in the auditory domain for LFL participants.

Discussion

The present exploratory study provided three central findings. First, children with FL showed reduced subcortical volumes of limbic structures, specifically the thalamus and amygdala, within the same hemisphere of their lesion, regardless of whether the insult included the subcortical substrates. Second, RFL and LFL children generally displayed altered white matter tissue properties within the limbic network and limbic-cortical circuits (i.e., lower FA and higher MD of the fornix and ATR), particularly ipsilateral to the lesion after covarying for the presence of subcortical insult. Importantly, ipsilateral measures of microstructural “immaturity” of the limbic circuits were associated with weaker visual emotion-perception in RFL children, whereas, similar fiber tract measures of the affective-processing network in the left hemisphere were related to less accurate performance in auditory emotion-discrimination in LFL youth. Altogether, these results suggest that the cerebral hemispheres are linked to emotion-processing based on specific modalities.

As expected, children with FL showed reduced volumes and altered microstructural tissue properties of white matter tracts within emotion-processing systems, particularly on the same side as the lesion. Notably, this pattern was observed regardless of controlling for presence of subcortical insult. Although these observations are likely due to a high number of participants with such injuries (i.e., half our FL sample size), findings also provide

support that early severe brain injuries may result in additional volume loss and weakened fiber tracts of adjacent regions (Beauchamp et al., 2011; Keightley et al., 2014), through subsequent necrosis, inflammatory responses, and apoptosis (for a review see Robertson, Scafidi, McKenna, & Fiskum, 2009; Yeates et al., 2012). However, unexpectedly, participants with right and left FL did not differ significantly in emotion-discrimination of auditory or visual stimuli relative to TD peers, which sharply contrasted with the limited existing developmental literature on this topic (Trauner et al., 1996; Stiles et al., 2005). Diverging findings between our study versus the aforementioned investigations likely stem from differences in the demographic background of participants recruited, task design, and operationalization of emotion-perceptual processes. First, it is likely that the tasks employed in our study required low effort or cognitive load, therefore reducing the discriminative sensitivity across clinical and non-clinical groups. Second, our studies broadly assessed emotion perception across visual and auditory modalities, devoid of linguistic aspects (e.g., verbal content, prosody), whereby, Trauner et al. (1996) examined affective and linguistic prosody across right and left FL children. These differences in the task design and affective indices likely contribute to disparate findings between investigations. Although no group differences were observed in emotion-discrimination across sensory or social modalities, it should be emphasized that our preliminary investigation had a low sample size of right versus left FL participants, which likely contributed to lower statistical power. As such, while these findings may warrant subsequent investigations in the neuroplasticity of emotion processing in children, we remain cautious in recognizing the limitations of our low participant pool, and subsequently, the possible high variance in our data. Therefore, in brief, future research would benefit from providing emotion-perception tasks of varying levels of difficulty, and greater recruitment of children with localized brain injuries.

Importantly, FL children in this study showed preserved emotion-perceptual functioning, which may reflect neuroplastic processes as they mature. In contrast to studies reported in Stiles and colleagues (2005), which included infant and preschool participants, our participant groups were on average 10 years of age. It is possible discrepancies between our results with those reported in Stiles et al. (2005) stem from functional reorganization that occur overtime as the child matures. Specifically, given affective discrimination is necessarily in daily social and behavioral functioning, the constant application of these skills post-insult may contribute to compensatory and maturational processes such as synaptogenesis, apoptosis, and arborization that may strengthen it over time (i.e., youth with earlier deficits may catch up in later developmental periods). Lastly, it is also possible that the neuroanatomical alterations found in our FL participants represent part of a developmental neural reorganization process that in turn explains their relatively intact emotion perceptual skills. To better understand these neuroplastic changes, future researchers would need to consider more extensive, longitudinal investigations of youth affected by unilateral brain damage, as specific timing of the insult also contribute to the degree emotion-processing functions are preserved or recovered (Cioni, Acunto, & Guzzetta, 2011).

Of note, the additional analyses involving two participants with weaker emotion-perceptual skills than their FL and TD counterparts provide limited evidence that greater neural insult, as represented by more volume loss and weaker fiber integrity, of the limbic network likely

contribute to more limitations in functional and neural re-organization. Furthermore, based on the MRI and DTI measures, the individual RFL participant with weaker visual emotion discrimination showed bilateral neural aberrations, broadly suggesting that affect perception, particularly of the visual modality, may be more diffused rather than lateralized. Furthermore, the specific neuroanatomical anomalies of limbic structures ipsilateral to brain region involved in the individual LFL participant may possibly suggest lateralization of auditory emotion perception to the left hemisphere. These combined findings are in contrast to the right-hemisphere model (Demaree, Everhart, Youngstrom, & Harrison, 2005) or the right-hemisphere emotion-processing hypothesis (Borod et al., 2002), which generally implicated the right hemisphere as the center of affective-processing skills. Instead, results indicate that neural regions dedicated to emotion processing potentially differ as a function of sensory modality. Notably, given these findings are based on two individual cases, a larger sample size of FL participants with more variability in functional skills and affected brain regions will be needed to better understand the neural and functional organization of emotion processing across specific sensory modalities.

Among FL children, performance across visual versus auditory emotion processing was linked to the hemisphere of the lesion. Similar to those noted above, findings were partially in contrast to the right hemisphere emotion-processing hypothesis (Borod et al., 2002). Although white matter integrity of right fornix and ATR were broadly associated with visual emotion-perception among RFL children, this relationship was not observed for the LFL group. Consistent with Kucharska-Pietura et al. (2003), we observed an association between fiber integrity of limbic circuits within the left hemisphere, particularly among LFL individuals, with their auditory emotion-perception. It is possible that the observed associations between anatomical and structural characteristics with different sensory emotion-perceptual performance across right and left FL groups represent unique neural and functional reorganization mechanisms that occur in early development after the injury. Moreover, the different associations may lend more credence to the interactive specialization hypothesis, which contends functional development emerges from interaction of various brain regions (Johnson et al., 2005). Therefore, the reorganization of emotion-processing networks may stem from activation of different brain regions after the neural insult (e.g., limbic-striatal, limbic-cortical, etc.), allowing specific circuits to strengthen and specialize in functional responses (Yeates et al., 2012). Findings highlight the significance of early social-emotional skills intervention for young children with neural insults, as early brain lesions have been linked to social dysfunction (Anderson, Rosema, Gomes, & Catroppa, 2012).

Differential associations between FA and MD of ATR with visual and auditory emotion perception were observed across right versus left FL children, suggesting this pathway may serve varying functions based on the hemispheric location of the brain injury. The ATR is a body of fibers projecting from the thalamus and connects limbic substrates to the frontal cortex (Mori et al., 2005). The ATR has been proposed to contribute to the motivational system (i.e., processing and response to reward and punishment) underpinning depression (Coenen et al., 2012), and involved in the cortical control of emotions (Papez, 1937). Importantly, disruptions in structural integrity of ATR have been linked to deficits in affective self-awareness (alexithymia) among patients with severe mental illness (Kubota et al., 2012). Additionally, DTI indices of ATR have been linked to emotional empathy

(Parkinson & Wheatley, 2014). Taken together, the current findings suggest that neurologic disruptions in the ATR from organic brain disturbances may reshape brain-behavioral relationships and impact the subjective experience and response to different emotions, which in turn may contribute to impaired social- and emotion-perception (Dennis et al., 1998; Stiles et al., 1998).

It should also be noted that FA of the left fornix was associated with auditory-perception among the RFL group, whereas MD of the right fornix was related to visual emotion-discrimination of the LFL children. The fornix is the nexus between the hippocampus and mammillary bodies, and is part of the limbic system (Concha, Gross, & Beaulieu, 2005). Notably, disruption within this body of fibers has been linked to bipolar disorder in adolescence (Barnea-Goraly et al., 2009), childhood- and adolescent-onset schizophrenia (Kendi et al., 2008), and chromosome 22q11.2 deletion syndrome (Deng et al., 2015), conditions linked to severe affective and functional impairments. Although associations between structural integrity of fornix and emotion-processing have not been well investigated, this white matter tract bundle has been implicated in memory deficits such as recognition memory (Aggleton et al., 2010; Thomas et al., 2011). It is possible that youth who experienced significant neural insult may have more difficulties with retrieving affective schemas and memories to use in the evaluation of emotional stimuli (Izard, 2009), which in turn adversely impacts their interpersonal skills and social success (Levin et al., 2004) and affect regulation and expression (Stiles et al., 1998). Consequently, the neural reorganization of brain-behavioral relationships in the fornix and ATR could contribute to the augmented risk of social dysfunction and psychopathology in youth with brain injuries (Duval et al., 2002; Max et al., 1997; 1998; 2002).

Furthermore, the septum and hippocampus are also strongly connected via the fornix, and the septal-hippocampal pathway has been implicated in anxiety and fear responses (Degroot & Treit, 2004). As shown in animal research, this pathway is involved in responding to punishment and threat by inhibiting behavior (Gray & Neil, 2003) and modulating anxiety (Parfitt et al., 2017), and accordingly, lesions within either septum or hippocampus have been associated with more disinhibited behaviors (Gray & Neil, 2003). Cholinergic and GABAergic fibers involved in the septal-hippocampal system have also been implicated in the memory functioning, specifically selection and formation (Micheau & Marighetto, 2011). Accordingly, children with significant brain injuries may also experience reorganization within this system that interferes with their ability to learn and respond to social dangers, which subsequently impacts their self-regulation and emotion reactivity (Levin et al., 2004; Stiles et al., 1998).

Notably, the present investigation was exploratory, and had several limitations that should be considered in subsequent research. Importantly, as indicated above, future investigations should include a larger number of child participants with FL to increase the sensitivity of detecting effects. Additionally, several recent studies have shown that the developmental timing of the brain insult and the severity poses different risks to functional brain recovery (Anderson et al., 2011). The type of interventions and exposure to enriched home environments should also be considered. As reviewed by Anderson and colleagues (2011), recovery should be considered in a continuum whereby risks, such as the timing of the

injury, severity of insult, location and extent of the damage, and source of the injury, and possible factors building resiliency (e.g., interventions, family support, degree of medical care post-insult) need to be assessed to determine developmental outcomes. Future researchers will also need to apply developmental approaches such as the use of longitudinal designs to investigate functional brain development. Additionally, as seen in Table 2, our limited FL participant group had significant variation in the location of neural insult leaving it impossible to fully disentangle degree of functional reorganization of the emotion-processing system across right versus left FL groups. Greater recruitment of FL children – both in terms of sample size and in diversity of neural insult – will also be necessary to better determine whether damage to specific lateralized regions are linked to more impaired emotion-processing, or alternatively, to more functional recovery. Finally, to adequately address the empirical questions related to the lateralization of social-emotional processing skills, future developmental research with children with neural insults will need to integrate interdisciplinary methods (e.g., cytoarchitectonic measures, behavioral responsivity, neuroimaging measures) to better understand the mechanisms associated with the recovery and reorganization of social functions. Multilevel and developmental approaches would be essential to characterize functional development for children with FL, which in turn can inform intervention programs. Moreover, such investigative efforts provide additional opportunities to examine the efficacy of customized interventions for FL children across developmental periods.

In summary, to our knowledge, the current study is the first investigative effort to examine brain-behavior differences related to emotion processing in children with right versus left neural insult. Our findings suggest that children with right FL, as compared to those with left lesions, show gray matter morphological and white matter tissue property alterations within the emotion circuitry ipsilateral to the insult that are more strongly associated with weaker visual and auditory emotion-processing respectively. However, given our small sample size, these preliminary findings should be considered as groundwork to guide subsequent larger-scale research on the neurodevelopmental plasticity of emotion processing skills.

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Table 1

Participant Characteristics.

	Typically Developing (n=13)	Focal Lesion (n=13)	
		Right Hemispheric Lesion (n=7)	Left Hemispheric Lesion (n=6)
Age (years)	10.16 (2.13)	10.17 (3.02)	10.09 (1.86)
Gender	5F	2F	3F
FIQ	114.08 (7.32)	98.42 (18.63)	87.17 (12.54)
VIQ	117.85 (7.79)	104.14 (15.23)	91.50 (14.53)
PIQ	107.38 (10.72)	92.43 (20.07)	85.00 (10.71)
Subcortical Lesion	---	n=4	n=4
Visual Emotion Discrimination (VED)(% correct)	94.38(3.93)	89.58(9.03)	90.83(5.63)
Social VED	95.83(6.21)	88.19(13.54)	92.50(7.45)
Non-social VED	92.92(6.23)	90.97(4.87)	89.17(5.59)
Auditory Emotion Discrimination (AED)(% correct)	91.29(8.06)	86.11(9.19)	81.25(12.15)
Social AED	93.33(6.27)	92.36(4.87)	88.33(12.29)
Non-social AED	89.58(11.50)	79.86(17.76)	74.17(13.63)

Note. One RFL, one LFL participant, and three TD participants did not complete the discrimination task.

Table 2

Brain Lesion Information.

Participant	Lesion Site (Hemisphere)	Subcortical Lesion	Lesion information
1	R	Y	Focal enlargement posterior right lateral ventricle; small band of heterotopic gray matter on the right hemisphere
2	R	Y	Encephalomalacia with right periventricular white matter in frontal region
3	R	N	Focal encephalomalacia of right parietal lobe with rim of gliosis
4	R	Y	Right frontal porencephalic cyst with surrounding gliosis
5	R	N	Right hemisphere hemiatrophy
6	R	Y	Right perventricular leukomalacia
7	R	N	Schizencephaly right frontal and parietal regions
8	L	N	Encephalomalacia left frontal lobe superior to sylvian fissure
9	L	Y	Encephalomalacia left parietal lobe; compensatory enlargement left lateral ventricle
10	L	Y	Left posterior porencephaly; enlargement posterior left lateral ventricle
11	L	Y	Ulegyria left posterior sylvian fissure with associated gliosis
12	L	Y	Focal porencephaly superior aspect left lateral ventricle
13	L	N	Encephalomalacia left temporal lobe with compensatory porencephaly left lateral ventricle

Table 3

Average Subcortical Volume of the Amygdala, Hippocampus, and Thalamus in Children with Right or Left Hemispheric Lesions (N=13) and Typically Developing Participants (N=13).

Subcortical Volume (mm^2)	**Right Hemispheric Lesion (N=7)**	**Left Hemispheric Lesion (N=6)**	**Typical Development (N=13)**	***p-values***
Amygdala (r/l)	1522.29/ 1572.14	1694.67/ 1371.33	1589.85/ 1497.46	0.059/ 0.134
Hippocampus (r/l)	3838.71/ 4073.43	3713.50/ 2975.00	4104.69/ 4006.31	0.599/ 0.030 *
Thalamus (r/l)	5210.57/ 7135.14	7128.50/ 5713.50	7153.31/ 6944.77	0.001 **/ 0.001 **

* $p < .05$

** $p < .01$

*** $p < .001$

Table 4

Average Fractional Anisotropy and Mean Diffusivity of Fornix and Anterior Thalamic Radiation in Children with Right or Left Hemispheric Lesions (N=13) and Typically Developing Participants (N=13).

	Right Hemispheric Lesion (N=7)	Left Hemispheric Lesion (N=6)	Typical Development (N=13)	*p-values*
Fornix (r/l)				
Fractional Anisotropy	0.269/ 0.303	0.299/ 0.250	0.311/ 0.311	0.013 *, / 0.003 **
Mean Diffusivity	1.252/ 1.050	1.067/ 1.268	1.030/ 1.037	0.004 **, / 0.031 *
Anterior Thalamic Radiation (r/l)				
Fractional Anisotropy	0.318/ 0.335	0.362/ 0.351	0.362/ 0.369	0.140/ 0.011 *
Mean Diffusivity	0.911/ 0.836	0.807/ 0.830	0.816/ 0.809	0.261/ 0.508

* $p < .05$

** $p < .01$

*** $p < .001$

Table 5

Average *subcortical volume and fiber integrity of the limbic network across typically developing (TD) group, right and left focal lesion (RFL, LFL) children, and two FL participants with outlying emotion-discrimination data of at least two standard deviations.*

	RFL Participant (RFL-O)	LFL Participant (LFL-O)	Remaining RFL Children	Remaining LFL Children	TD Participants	Significant Comparison
Emotion Discrimination (% correct)						
Visual	77.08	87.50	92.08	91.67	94.38	RFL-O < RFL, TD
Auditory	79.17	60.42	87.50	86.45	91.29	LFL-O < LFL, TD
Subcortical Volume (mm^2)						
Amygdala (r/l)	1201/ 1566	1561/ 1246	1575.83/ 1573.17	1721.40/ 1396.40	1589.85/ 1497.46	Right: RFL-O < RFL
Hippocampus (r/l)	2803/ 3368	4257/ 2774	4011.33/ 4191.00	3604.80/ 3015.20	4104.69/ 4006.31	Right: RFL-O < RFL, TD, Left: RFL-O < RFL LFL-O < TD
Thalamus (r/l)	3502/ 5501	7036/ 3757	5495.33/ 7407.50	7147.00/ 6104.80	7153.31/ 6944.77	Right: RFL-O < TD Left: RFL-O < RFL LFL-O < LFL, TD
Fractional Anisotropy						
Fornix (r/l)	0.229/ 0.274	0.294/ 0.152	0.276/ 0.309	0.299/ 0.269	0.311/ 0.311	Right: RFL-O < TD Left: RFL-O < RFL, TD LFL-O < LFL, TD
Anterior Thalamic Radiation (r/l)	0.223/ 0.286	0.376/ 0.274	0.337/ 0.345	0.359/ 0.367	0.362/ 0.369	Right: RFL-O< RFL, TD Left: RFL-O < RFL, TD LFL-O < LFL, TD
Mean Diffusivity						
Fornix (r/l)	1.574/ 1.256	0.986/ 1.587	1.187/ 1.008	1.083/ 1.205	1.030/ 1.037	Right: RFL-O > RFL, TD Left: RFL-O > RFL, TD LFL-O >TD
Anterior Thalamic Radiation (r/l)	1.259/ 0.953	0.779/ 0.949	0.841/ 0.813	0.812/ 0.806	0.816/ 0.809	Right: RFL-O > RFL, TD Left: RFL-O > RFL, TD LFL-O > LFL, TD

Note. Comparisons whereby measures across groups are at least two standard deviations are listed in the “Significant Comparison” column.

Table 6

Associations Between DTI measures, and Visual and Auditory Emotion-Discrimination in Children with Focal Brain Damage (N=10).

	Right Hemispheric Lesion (N=5)		Left Hemispheric Lesion (N=5)	
DTI measures	**Visual Affect-Discrimination**	**Auditory Affect-Discrimination**	**Visual Affect-Discrimination**	**Auditory Affect-Discrimination**
Fractional Anisotropy				
Fornix (r/l)	0.910 */ 0.498	0.268/ 0.929 *	−0.626/ 0.079	−0.068/ 0.912 *
Anterior Thalamic Radiation (r/l)	0.933 */ 0.958 *	0.483/ 0.378	−0.644/ 0.173	−0.095/ 0.879 *
Mean Diffusivity				
Fornix (r/l)	−0.978 **/ −0.443	−0.339/ −0.667	0.933 */ 0.002	0.463/ −0.895 *
Anterior Thalamic Radiation (r/l)	−0.874 +/ −0.756	−0.546/ −0.633	0.690/ −0.310	0.774/ −0.896 *

+ $p = .05$

* $p < .05$

** $p < .01$