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Short communication

Atypical age-related changes in the structure of the mentalizing network in children with refractory focal epilepsy

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ABSTRACT

Refractory focal epilepsy (rFE) is commonly comorbid with impaired social functioning, which significantly reduces quality of life. Previous research has identified a mentalizing network in the brain—composed of the anterior temporal cortex, medial prefrontal cortex (mPFC), posterior temporal sulcus (pSTS), and temporoparietal junction—that is thought to play a critical role in social cognition. In typically-developing (TD) youth, this network undergoes a protracted developmental process with cortical thinning and white matter expansion occurring across adolescence. Because epilepsy is associated with both social dysfunction and irregular neural development, we investigated whether gray and white matter in the mentalizing network differed between youth with rFE (n = 22) and TD youth (n = 41) aged 8–21 years. Older age was associated with reduced cortical thickness in the bilateral mPFC in TD youth, but not in rFE youth. Compared to TD youth, rFE youth had greater white matter density in the right pSTS. Our findings suggest that rFE youth show atypical patterns of cortical thickness and white matter density in regions of the brain that are typically associated with social information processing, potentially as a result of ongoing seizures, comorbid conditions, or other illness-related factors. These results encourage future research to examine whether such variations in neural structure are predictive of specific social deficits in rFE youth.

1. Introduction

Medically refractory focal epilepsy (rFE), or drug-resistant epilepsy that is localized to one region of the brain, is associated with neurocognitive problems that substantially impact quality of life (Hermann et al., 2000). Deficits in mentalizing and social cognitive abilities are particularly common in children with rFE and commonly comorbid syndromes like autism (Stewart et al., 2019). Understanding potential neural mechanisms underlying social cognition deficits should be a focus of pediatric epilepsy research.

Mentalizing, or the ability to infer others' intentions and subjective states, is thought to be supported by a network comprised of the medial prefrontal cortex (mPFC), temporoparietal junction (TPJ), posterior superior temporal sulcus (pSTS), and anterior temporal cortex (ATC) (Mills et al., 2014). Structural and diffusion MRI studies find decreases in cortical thickness (CT) and increases in white matter (WM) volume/integrity in these areas during adolescence (Mills et al., 2014; Wang et al., 2018), suggesting that experience-guided pruning and axonal myelination may underlie functional gains in mentalizing across development (Burnett et al., 2011).

The excitotoxicity of seizures or other neuropathology associated with epilepsy could result in altered neurodevelopment. Atypical cortical thinning and WM expansion are often found in concurrent and prospective studies of brain development in youth with focal epilepsy (Bonilha et al., 2010; Boutzoukas et al., 2020; Hermann et al., 2010; Tosun et al., 2011). Given evidence that youth with epilepsy often

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struggle with social cognitive skills (Stewart et al., 2019) and may undergo different neurodevelopmental trajectories than their peers (e.g., Swann, 2004), we examined potential structural differences between youth with and without rFE in regions of the brain that have been tightly linked to mentalizing ability.

Specifically, we investigated age-related changes in gray matter (GM) and WM within the mentalizing network in youth with rFE and typically-developing (TD) youth. To boost statistical power, we constrained our analyses to regions of interest (ROIs) within this network, which has a well-established role in mentalizing functions (Mills et al., 2014; Kilford et al., 2016). We also included the amygdala as an ROI, as pathology in this area is common in people with epilepsy and this region plays a role in social cognition (Aroniadou-Anderjaska et al., 2008). Although we did not formally assess mentalizing in this study, other studies from this sample have found deficits in emotion recognition, (Morningstar et al., 2020) and prior work has established a high frequency of mentalizing difficulties in youth with rFE (e.g., Lunn et al., 2015). Our aim was to a) establish whether there are differential age-related changes in the structure of the mentalizing network in youth with and without rFE, and b) explore whether different ROIs or metrics (GM or WM) show specific vulnerability.

2. Materials and methods

2.1. Participants

Participants were part of a larger functional MRI study. The sample included 41 TD youth with no known history of neurologic or psychiatric conditions and 26 youth with rFE. Youth with rFE were recruited through the epilepsy unit of a children's hospital and TD youth were recruited through flyers emailed to hospital employees. Informed consent/assent was obtained, and all procedures were approved by the Institutional Review Board. Eligibility criteria included age of 8–21 years and ability to complete a non-sedated MRI session. Demographic and disease variables are reported in Table 1. All rFE youth had failed at least two drug treatments and underwent a thorough assessment (MRI, PET, long-term EEG monitoring, and review of seizure semiology) to obtain epilepsy classifications. No participant was diagnosed with autism or intellectual disability. Three rFE youth were excluded due to prior surgical resection. rFE and TD youth did not differ in age, $t(61)$=-0.13, $p = .90$, ethnicity, $\chi^2(3, 63) = 2.01$, $p = .57$, or gender distribution, $\chi^2(1, 63) = 3.48$, $p = .06$. Participants with a variety of epileptogenic zones were included due to previous research demonstrating that seizure foci were not differentially related to social deficits (Stewart et al., 2019).

Table 1
Demographic Information and Disease-Related Variables.

	Typically-developing youth (n = 42)	Youth with epilepsy (n = 22)
Age (in years)	14.42 (3.32)	14.53 (3.53)
Gender	16 male (39.02 %)	14 male (63.64 %)
Ethnicity		
White	28 (68.29 %)	13 (59.09 %)
Black	9 (21.95 %)	4 (18.18 %)
Asian	1 (2.44 %)	1 (4.55 %)
Multi-ethnic	3 (7.32 %)	4 (18.18 %)
Age of epilepsy onset	–	6.89 (4.37)
Duration of epilepsy	–	7.65 (3.92)
Presence of MTS	–	7 (31.82 %)
Number of AEDs	–	2.82 (1.33)
Epilepsy type		
Temporal	–	14 (63.64 %)
Fronto-temporal	–	2 (9.09 %)
Frontal	–	4 (18.18 %)
Other	–	2 (9.09 %)
Epilepsy lateralization		
Left	–	10 (45.45 %)
Right	–	10 (45.45 %)
Bilateral	–	2 (9.09 %)

Note. MTS = mesial temporal sclerosis. AED = anti-epilepsy drug. Mean (standard deviation) of age at scan, age of epilepsy onset, duration of epilepsy are reported in years; mean (standard deviation) for number of AEDs prescribed at time of study are also reported. Other values represent the number of participants (%) in each category. One participant in the 'Other' epilepsy group had occipital epilepsy and the other is indeterminant.

2.2. MRI acquisition and preprocessing

The MRI protocol included a T1-weighted anatomical scan and a diffusion weighted sequence. Imaging protocol and preprocessing details are included in Supplemental Materials.

2.3. Analysis

We restricted analysis to the amygdala and regions of interest (ROIs) in the mentalizing network: the bilateral ATC, mPFC, pSTS, and TPJ. Publicly available masks (Mills et al., 2014) were overlaid onto the cortical segmentation for each participant. Average CT across all vertices in each ROI were computed for each participant. For the amygdala, volume rather than CT was calculated and divided by intracranial volume to control for variability in head size. For tractography, each ROI mask was transformed into participant's native diffusion space and used as both seed and target. Probabilistic tractography was used to determine fiber counts using probtrackx2 (Behrens et al., 2007). In an iterative fashion each ROI was used as a seed and fiber counts to the remaining ROIs in the network were calculated. The streamline counts in each seed voxel were adjusted for the total number in each seed region to calculate the estimate of fibers going from each ROI to the rest of the network (Behrens et al., 2007; Tomassini et al., 2007).

The final sample included 41 TD (40 for WM) and 22 rFE youth. For each measure, separate general linear models were performed to examine associations between *Group* (between-subjects variable: rFE vs. TD), *Age* (between-subjects continuous variable, in years), and *Group x Age*. Significant interactions were probed using simple slopes tests (Dawson, 2014). Gender and scanner were included as nuisance covariates in all analyses.

3. Results

3.1. Gray matter

There were no *Group* main effects in GM measures (Table 1). *Age* effects reflect reduced cortical thickness in older youth compared to younger youth across groups in the bilateral pSTS, mPFC, and TPJ. A significant *Group x Age* effect emerged in the bilateral mPFC: thickness decreased with age for TD youth, left mPFC: $t(57)$=-4.88, $p < .001$, right mPFC, $t(57)$=-4.88, $p < .001$, but not for rFE youth, left mPFC: $t(57)$=-0.81, $p = .42$, right mPFC: $t(57)$=-0.86, $p = .40$ (Fig. 1). A whole-brain analysis is included in Supplemental Materials.

3.2. White matter

A group effect was found reflecting *greater* number of outgoing fibers from the right pSTS to the mentalizing regions in rFE group. There was also a main effect of *Age* in the left TPJ, where outgoing fibers increased with age across groups. There was a trend-level effect of *Group x Age* in the left mPFC ($p = .06$) where controls exhibited increases in outgoing fibers with age, $t(56) = 2.61$, $p = .01$, but rFE youth didnot, $t(56)$=-0.64, $p = .53$(Table 2).

4. Discussion

The current study compared age-related changes in GM and WM

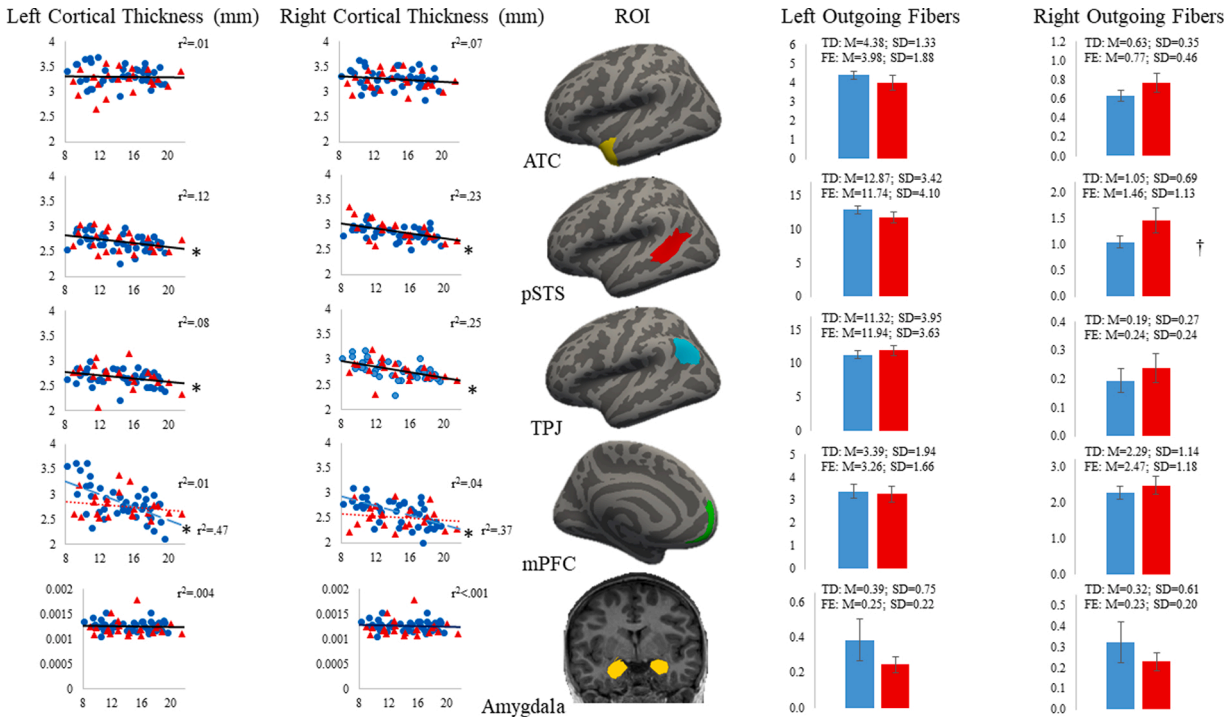

Fig. 1. *Average Cortical Thickness, Volume and Number of Outgoing Fibers in each ROI.*
Note. TD = typically developing. FE = focal epilepsy. ATC = anterior temporal cortex. mPFC = medial prefrontal cortex (medial Brodmann Area 10). pSTS = posterior superior temporal sulcus. TPJ = temporoparietal junction. r^2=coefficient of determination. Blue circles represent TD youth; red triangles represent FE youth. *x*-axes represent age in years; *y*-axes represent average cortical thickness in millimeters (mm), average volume in mm^3 for the amygdala, or number of outgoing fibers in millions. Blue, dashed lines represent trendlines for TD youth. Red, dotted lines represent trendlines for FE youth. Black solid lines represent trendlines for data collapsed across groups. * denotes trendlines with slopes that are significantly different from 0 (details provided in text). Bar graphs are provided for white matter data to better illustrate group differences. Blue bars represent average number of outgoing fibers for TD youth. Red bars represent average numbers of outgoing fibers for FE youth. Error bars represent standard error of the mean. † indicates significant group differences at $p < .05$.

Table 2
Effects of Group, Age, and Group x Age on Cortical Thickness/Volume and Outgoing White Matter Fibers for each ROI.

Cortical Thickness/Volume								Outgoing White Matter Fibers					
		Left			Right			Left			Right		
ROI		*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
	Group	3.10	.08	.05	1.05	.31	.02	.26	.61	.01	2.16	.15	.04
ATC	Age	.004	.95	<.001	1.42	.24	.02	.02	.89	<.001	2.22	.14	.04
	G x A	1.83	.18	.03	.40	.53	.01	.47	.50	.01	1.58	.21	.03
	Group	.86	.36	.02	2.21	.14	.04	.01	.92	<.001	.75	.39	.01
mPFC	Age	13.29	<.001*	.19	13.43	.001*	.19	.96	.33	.02	.89	.35	.02
	G x A	5.59	.02*	.09	5.59	.02*	.09	3.61	.06	.06	2.30	.14	.04
	Group	.07	.80	.001	2.90	.09	.05	.44	.51	.01	4.92	.03*	.08
pSTS	Age	8.83	.004*	.13	26.30	<.001*	.32	.25	.62	.004	1.27	.27	.02
	G x A	.01	.91	<.001	2.19	.15	.04	1.21	.28	.02	.36	.55	.01
	Group	1.39	.24	.02	.15	.70	.003	1.52	.22	.03	.66	.42	.01
TPJ	Age	7.15	.01*	.11	21.56	<.001*	.27	5.45	.02*	.09	.04	.85	.001
	G x A	.18	.67	.003	.88	.35	.02	1.00	.32	.02	.61	.44	.01
	Group	1.92	.17	.03	3.42	.07	.06	.25	.62	.01	.23	.63	.004
Amygdala	Age	.23	.63	.004	.22	.64	.004	.31	.58	.01	.07	.80	.001
	G x A	.04	.85	.001	.50	.48	.01	.002	.97	<.001	.01	.93	<.001

Note. *$p < .05$. η_p^2=partial eta squared. G x A = Group x Age interaction. ATC = anterior temporal cortex. mBA10=medial Brodmann Area 10 (medial prefrontal cortex). pSTS = posterior superior temporal sulcus. TPJ = temporoparietal junction.

within a mentalizing brain network in youth with and without rFE. Age-related effects in the pSTS and TPJ indicate comparable patterns of cortical thickness across adolescence in both groups, while lack of age effects in either group in the ATC or amygdala could reflect a more subtle pattern of development that was not detectable in our sample (Mills et al., 2014; Uematsu et al., 2012).

TD and rFE youth exhibited a differential pattern of age-related change in cortical thickness in the mPFC. Age was associated with reduced thickness in TD youth, but not in rFE youth. These differences may reflect early pathological effects of epilepsy or other neuropathological conditions that predispose for the emergence of epilepsy (Hermann et al., 2000). Because this is a cross-sectional study, conclusions about the causal role of epilepsy cannot be drawn. However, we believe these results may point to potential biomarkers of functional disability that are common in the rFE population. It is noteworthy that the mPFC was the only area in the mentalizing network where developmental

trajectories differed across groups, despite the fact that most rFE participants had a temporal epileptogenic zone. This pattern is consistent with other studies examining cortical thickness in children with focal epilepsy (e.g., Boutzoukas et al., 2020; Hermann et al., 2010), suggesting that fronto-cortical GM maturation may be especially vulnerable to seizures, anti-epilepsy drugs, or other disease-related factors (Bernhardt et al., 2013; Widjaja et al., 2011). However, it is possible that the lack of findings in the temporal lobe (akin to those reported in previous work; Bernhardt et al., 2013) could be a result of heterogeneity in our study population or modest sample size.

Probabilistic tractography revealed a different pattern. TD youth had fewer outgoing fibers in the right pSTS than rFE youth. Because groups did not differ in cortical thickness in this ROI, it is possible that abnormalities in WM density precede abnormalities in GM here (Hutchinson et al., 2010). There was also a trend-level effect in the mPFC where TD youth demonstrated typical age-related increases in WM density with age, but rFE youth did not. This aligns with GM results, in that rFE youth are not exhibiting the same age-related changes in neural development in frontal regions as TD youth (Hermann et al., 2010; Tosun et al., 2010).

A major shortcoming of this study is the lack of formal mentalizing assessment. As a result, it is difficult to draw specific conclusions about the association between group differences in brain structure and social functioning. The current results seem to suggest that, within the mentalizing network, the structural integrity of frontal areas may be more affected by rFE or other comorbid pathology than other regions. The functional implications of this are unclear, but studies parsing specific aspects of mentalizing may be informative (Schurz et al., 2020). Replicating these findings in a longitudinal framework and integrating behavioral measures with a larger sample of TD and rFE youth will be important for understanding how these differences in brain structure emerge and how they are reflected in specific social deficits.

5. Conclusion

rFE youth showed altered different patterns of age-related changes in cortical thickness and a trend for reduced WM connections in the mPFC, as well as greater WM fiber density in the right pSTS, relative to TD youth. These findings are consistent with emerging work highlighting altered neurodevelopment in youth with rFE. Further probing this phenomenon may help identify the individuals most at risk for social deficits and provide valuable insights into the pathophysiology of an important behavioral difficulty encountered by youth with chronic epilepsy.

Ethics statement

Informed consent was obtained for experimentation with human subjects. All work described has been carried out in accordance with the Declaration of Helsinki for experiments involving humans.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2021.106701.

References

Aroniadou-Anderjaska, V., Fritsch, B., Qashu, F., Braga, M.F., 2008. Pathology and pathophysiology of the amygdala in epileptogenesis and epilepsy. Epilepsy Res. 78 (2–3), 102–116. https://doi.org/10.1016/j.eplepsyres.2007.11.011.

Behrens, T.E., Berg, H.J., Jbabdi, S., Rushworth, M.F., Woolrich, M.W., 2007. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? Neuroimage 34 (1), 144–155. https://doi.org/10.1016/j.neuroimage.2006.09.018.

Bernhardt, B., Hong, S.J., Bernasconi, A., Bernasconi, N., 2013. Imaging structural and functional brain networks in temporal lobe epilepsy. Front. Hum. Neurosci. 7, 624. https://doi.org/10.3389/fnhum.2013.00624.

Bonilha, L., Edwards, J.C., Kinsman, S.L., Morgan, P.S., Fridriksson, J., Rorden, C., Rumboldt, Z., Roberts, D.R., Eckert, M.A., Halford, J.J., 2010. Extrahippocampal gray matter loss and hippocampal deafferentation in patients with temporal lobe epilepsy. Epilepsia 51 (4), 519–528. https://doi.org/10.1111/j.1528-1167.2009.02506.x.

Boutzoukas, E.M., Crutcher, J., Somoza, E., Sepeta, L.N., You, X., Gaillard, W.D., Wallace, G.L., Berl, M.M., 2020. Cortical thickness in childhood left focal epilepsy: thinning beyond the seizure focus. Epilepsy Behav. 102, 106825 https://doi.org/10.1016/j.yebeh.2019.106825.

Burnett, S., Sebastian, C., Kadosh, K.C., Blakemore, S.J., 2011. The social brain in adolescence: evidence from functional magnetic resonance imaging and behavioural studies. Neurosci. Biobehav. Rev. 35 (8), 1654–1664. https://doi.org/10.1016/j.neubiorev.2010.10.011.

Dawson, J.F., 2014. Moderation in management research: what, why, when and how. J. Bus. Psychol. 29, 1–19. https://doi.org/10.1007/s10869-013-9308-7.

Hermann, B.P., Seidenberg, M., Bell, B., 2000. Psychiatric comorbidity in chronic epilepsy: identification, consequences, and treatment of major depression. Epilepsia 41, S31–S41. https://doi.org/10.1111/j.1528-1157.2000.tb01522.x.

Hermann, B.P., Dabbs, K., Becker, T., Jones, J.E., y Gutierrez, A.M., Wendt, G., Koehn, M. A., Sheth, R., Seidenberg, M., 2010. Brain development in children with new onset epilepsy: a prospective controlled cohort investigation. Epilepsia 51 (10), 2038–2046.

Hutchinson, E., Pulsipher, D., Dabbs, K., y Gutierrez, A.M., Sheth, R., Jones, J., Seidenberg, M., Meyerand, E., Hermann, B., 2010. Children with new-onset epilepsy exhibit diffusion abnormalities in cerebral white matter in the absence of volumetric differences. Epilepsy Res. 88 (2–3), 208–214. https://doi.org/10.1016/j.eplepsyres.2009.11.011.

Kilford, E.J., Garrett, E., Blakemore, S.J., 2016. The development of social cognition in adolescence: an integrated perspective. Neurosci. Biobehav. Rev. 70, 106–120. https://doi.org/10.1016/j.neubiorev.2016.08.016.

Lunn, J., Lewis, C., Sherlock, C., 2015. Impaired performance on advanced Theory of Mind tasks in children with epilepsy is related to poor communication and increased attention problems. Epilepsy Behav. 43, 109–116. https://doi.org/10.1016/j.yebeh.2014.11.010.

Mills, K.L., Lalonde, F., Clasen, L.S., Giedd, J.N., Blakemore, S.J., 2014. Developmental changes in the structure of the social brain in late childhood and adolescence. Soc. Cogn. Affect. Neurosci. 9 (1), 123–131. https://doi.org/10.1093/scan/nss113.

Morningstar, M., Hung, A., Grannis, C., French, R.C., Mattson, W.I., Ostendorf, A.P., Gedela, S., Englot, D.J., Nelson, E.E., 2020. Blunted neural response to emotional faces in the fusiform and superior temporal gyrus may be marker of emotion recognition deficits in pediatric epilepsy. Epilepsy Behav. 112, 107432 https://doi.org/10.1016/j.yebeh.2020.107432.

Schurz, M., Radua, J., Tholen, M.G., Maliske, L., Margulies, D.S., Mars, R.B., Sallet, J., Kanske, P., 2020. Toward a hierarchical model of social cognition: a neuroimaging meta-analysis and integrative review of empathy and theory of mind. Psychol. Bull. https://doi.org/10.1037/bul0000303.

Stewart, E., Lah, S., Smith, M.L., 2019. Patterns of impaired social cognition in children and adolescents with epilepsy: the borders between different epilepsy phenotypes. Epilepsy Behav. 100, 106146 https://doi.org/10.1016/j.yebeh.2019.01.031.

Swann, J.W., 2004. The effects of seizures on the connectivity and circuitry of the developing brain. Ment. Retard. Dev. Disabil. Res. Rev. 10 (2), 96–100. https://doi.org/10.1002/mrdd.20018.

Tomassini, V., Jbabdi, S., Klein, J.C., Behrens, T.E., Pozzilli, C., Matthews, P.M., Rushworth, M.F.S., Johansen-Berg, H., 2007. Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. J. Neurosci. 27 (38), 10259–10269. https://doi.org/10.1523/JNEUROSCI.2144-07.2007.

Tosun, D., Dabbs, K., Caplan, R., Siddarth, P., Toga, A., Seidenberg, M., Hermann, B., 2011. Deformation-based morphometry of prospective neurodevelopmental changes in new onset paediatric epilepsy. Brain 134 (4), 1003–1014.

Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., Nishijo, H., 2012. Developmental trajectories of amygdala and hippocampus from infancy to

early adulthood in healthy individuals. PLoS One 7 (10), e46970. https://doi.org/10.1371/journal.pone.0046970.

Wang, Y., Metoki, A., Alm, K.H., Olson, I.R., 2018. White matter pathways and social cognition. Neurosci. Biobehav. Rev. 90, 350–370. https://doi.org/10.1016/j.neubiorev.2018.04.015.

Widjaja, E., Mahmoodabadi, S.Z., Snead I.I.I., O.C., Almehdar, A., Smith, M.L., 2011. Widespread cortical thinning in children with frontal lobe epilepsy. Epilepsia 52 (9), 1685–1691. https://doi.org/10.1111/j.1528-1167.2011.03085.x.