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The effects of sexual abuse on female adolescent brain structures

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Abstract

Objective: Sexual abuse (SA) is known for its effects on brain structures in adolescents. We aimed to explore if SA has any effect on limbic and prefrontal cortex (PFC) structures. We hypothesized that children with SA would have a thinner PFC with larger amygdala and hippocampus that lead to aberrations in threat detection, orientation and response circuit; that would be highly adaptive in a dangerous environment in the short term.
Method: We included 57 SA and 33 healthy control (HC) female participants. In addition to psychiatric evaluation, we acquired 3 T MR images from all participants. We compared prefrontal cortical thicknesses, hippocampus and amygdala volumes between groups.
Results: The age and education levels of study groups were matched, however, IQ scores and socioeconomic status (SES) scores of the SA group were lower than the controls. Total CTQ scores of the SA group were higher than the HC. Nevertheless, the mean value of sexual abuse scores was above the cut-off scores only for the SA participants. SA participants had larger right and left hippocampus and right amygdala volumes than the controls. SA group had reduced inferior frontal gyrus cortical thickness ($T=3.5$, $p<0.01$, cluster size=694 mm2, x=51 y=-30 z=6) than HC group. None of the structural findings were correlated with total or sexual abuse CTQ scores.
Conclusion: Children with SA history has structural abnormalities in threat detection, orientation and response circuit. SA victims with no psychiatric diagnosis have a high probability of psychiatric problems with a possible contribution of these aberrations. SA cases that do not have a diagnosis must not be overlooked as they may have structural changes in emotion related brain regions. Careful follow-up is needed for all of all SA cases.

Keywords: sexual abuse, cortical thickness, amygdala, hippocampus, prefrontal cortex

Introduction

Sexual abuse (SA) is one of the leading childhood adverse events (CAEs) among female adolescents which causes significant behavioral and educational difficulties in addition to health problems (1).
A recent study from Balkan Region reported that lifetime SA abuse rates varied between 7.6 and 18.6% and lifetime contact SA rates ranged from 3.6 to 9.8% of adolescents from 11 to 16 years old (2). It is established that CAEs including SA are related to a wide variety of psychiatric disorders and thus, CAEs constitute a major public health issue (3).

Effects of CAEs are well established in adults. Many neuroimaging studies confirmed brain structural changes in adults with a history of CAEs. The most replicated neuroimaging finding in adults

with CAEs is smaller hippocampal volumes independent of psychiatric disorder presence or type (4,5). On the other hand, structural neuroimaging research in children with CAEs suggest larger hippocampus and amygdala volumes that normalizes in the late adolescence or early adulthood (6–8). Moreover, studies in maltreated children revealed hyperactive amygdala irrespective of psychiatric diagnosis (9). It is suggested that the brain regions related to emotion networks mature early in abused children to accommodate the dangers in the vicinity more efficiently (10). Consequently, the modification of brain structure and functions allows the adjustment of reactions to constant threats (11).

Despite the short-term advantages of such an adaptive response for the child in an unpredictable environment, these changes may subserve hypervigilant and impulsive behaviors that lead to the immediate gratification or relief and also vulnerability for future psychiatric disorders (12). While PFC has regulatory and inhibitory functions on the limbic cortex, these functions may be maladaptive in children who are in a hazardous environment (12,13).

The interplay between PFC and limbic cortex (i.e. amygdala and hippocampus) is astoundingly complex in adolescence. In this period the cortical structure is refined and redundant neurons are eliminated through pruning which can be observed as cortical thinning. Pruning is suggested to improve computational power of the neocortex (14). Several research groups found PFC abnormalities in children and adolescents exposed to CAEs (15) and most of them found reduced lateral PFC (16,17) or orbitofrontal cortex (16,18,19), though one group found increased gray matter (GM) volume of anterior cingulate cortex (ACC) evident in a group of children exposed to CAEs before the age of 14 (20).

Nevertheless, cortical volumes may not capture the abnormalities in a developing brain. Newer techniques such as cortical thickness measurements (21) may reveal once obscure differences. Cortical thickness studies repeatedly indicated thinner lateral PFC, especially inferior frontal gyrus in children with CAEs (17,22–25). Since limbic system is found to be hyperactive in children with CAEs (26), a thinner PFC with larger amygdala and hippocampus would provide a computational advantage in a dangerous environment which would be highly adaptive in the short term (11,14). Therefore, in this study we aimed to measure hippocampus and amygdala volumes separately and explore whether there are any differences in cortical thickness of PFC. We preferred cortical thickness measurements as it gives more elaborate results in a developing neocortex (21). Conversely, volumetric measurements of amygdala and hippocampus would be reliable as they have archicortical or corticoid pattern (27).

Based on prior research we hypothesized that amygdala and hippocampus would be larger and PFC regions would be thinner in the sexually abused adolescents compared to their non-abused counterparts.

Material and Methods

Participants

All children who had SA referred to our department by the court order between 2013 and 2017 were evaluated for the eligibility to our study.

The study was approved by the local ethical review board (12-1.1/63). The workflow of the study starts with the application of the child with the court order.

A child and adolescent psychiatrist from our research team met the child and her legal representative or family and informed them about the study. The informed consent clearly explained that the psychiatric evaluation for judicial reasons and the current study are two unrelated processes; and declining to participate in the study has no impact on the forensic evaluation processes. After obtaining informed consent the same psychiatrist evaluated the participants and applied the psychometric tests except for the IQ tests.

Developmental and medical history of the participants are obtained from their families and medical records. The psychiatric evaluation process included The Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-SADS-PL) (28), Beck Depression Inventory (BDI) (29), the State-Trait Anxiety Inventory (STAI) (30), Childhood Trauma Questionnaire (CTQ) (31).

A psychologist applied the Wechsler Intelligence Scale for Children (WISC-R) (32) for the participants between the ages of 9-16 and the Wechsler Adult Intelligence Scale (WAIS-R) (33) for the participants after the age of 16. The Magnetic Resonance Imaging (MRI) scans were obtained in the same week and the same psychiatrist escorted the participants until all procedures end.

We contacted 134 participants with SA and 104 healthy controls for the study. Healthy control (HC) group was composed of female adolescents who responded to the local advertisements in schools. We included HCs with similar age and education levels to the sexually abused group. One hundred and fourteen sexually abused children and 38 HCs met the inclusion and exclusion criteria. Fifty-seven participants from the SA group and 33 HCs agreed for further evaluation in the study (mean age: 16.5± 0.2).

As sexually abused children are frequently victims of multiple kinds of trauma, children exposed to multiple kinds of trauma were not excluded. Exclusion criteria for both study groups were as follows: having an Intelligence Quotient (IQ) score

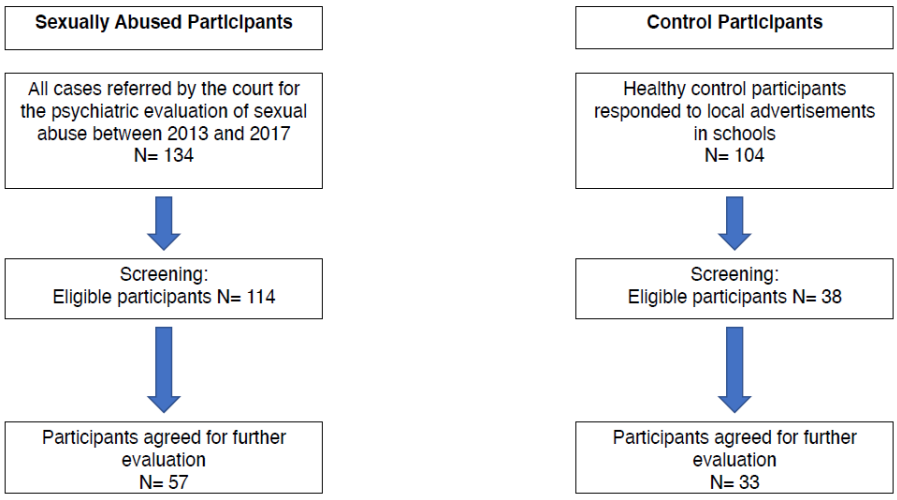

FIGURE 1. Flow diagram.

of 70 or below, a chronic medical illness like asthma or diabetes mellitus, a history of head injury with loss of consciousness longer than three minutes, any neurological illness, a pervasive developmental disorder, any personal or family history of psychotic disorders or bipolar disorder, a history of perinatal complications. Since previous studies reported that antidepressant medications may affect hippocampal volumes; we excluded participants that used antidepressants within four weeks prior to the study.

MRI Acquisition

MRI scans were performed on a 3 Tesla device (Siemens, Magnetom Verio, Erlangen, Germany) with 12-channel head coil. Turbo spin-echo T2-weighted, FLAIR and MPRAGE sequences were acquired in all participants.

To exclude any brain abnormalities, an experienced neuroradiologist evaluated images. MPRAGE sequences with 1 mm slice thickness, covering entire brain, was transferred to a personal computer for further structural analyses.

Amygdala and Hippocampus Volume Measurements and Cortical Thickness Analysis

We used FreeSurfer Software (ver.6.0 stable) (http://surfer.nmr.mgh.) for the processing of the images.

The process includes motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, and segmentation of the subcortical GM, white matter, cerebrospinal fluid, and volumetric structures. For the calculation of cortical thickness values for the whole brain surface we used recommended mainstream pipeline of FreeSurfer software.

Statistics and the final images derived from these segmentations are also a part of FreeSurfer pipeline outputs for regions of interest (34).

This method is an estimation of the probability for each voxel belonging to a certain structure which is based on a priori knowledge of spatial relationships obtained with a training set. It uses an extended (spatial nonstationary) Markov Random Field model for voxel intensities and spatial locations to locate and parcellate subcortical structures. This approach allows the probabilities to vary over space and be anisotropic. An article by Fischl et al (35) describes the stages of the processing.

Statistical Analysis

All sociodemographic and clinical variables were tested for a normal distribution by using Shapiro Wilk test and Levene's test for equality of variances. Comparisons between research and control groups according to the distribution of data were carried out by using Mann-Whitney U or t-test for sociodemographic and clinical variables.

Age and total intracranial volume were used as covariates in the one-way analysis of variance (ANOVA) for the hippocampus and amygdala volume comparisons.

We used General Linear Model to test the significance of cortical thickness difference between groups using age as an independent variable. Whole brain cortical thickness analyses were corrected for multiple comparisons using Monte Carlo simulation with $p<.01$ threshold and restricted to Frontal Lobe using ROIs extracted from Desikan-Killiany Atlas provided with FreeSurfer Software.

Results

Sociodemographic and Clinical Variables

There was no significant difference between groups, regarding age and education levels. However, IQ

scores and socioeconomic status (SES) scores of participants in the SA group were lower than the controls. All SA children were safe from their perpetrators and 80% (n=46) of the SA children were living with their family, 12.3% (n=7) with close relatives and 7% (n=4) were living in state facilities from the start of the judiciary process. Of all SA cases 15.8% (n=9) were abused by their father or elder brother, 7% (n=4) by their 2nd degree relatives and 77.2% (n=44) by non-relatives. 52.6% (n=30) of the SA group had one incident and 15.8 % (n=9) had two incidents, the remaining one third of the group had more than two incidents. 19.3 % (n=11) of the cases had SA before the age of 13 and 81.7% (n= 46) between 13-17 years of age.

Mean values for BDI, STAI and total CTQ scores of the SA group were higher than the control group. Although children in the abused group had higher scores in all CTQ subscales compared to controls, only the mean value of sexual abuse scores were above the cut-off scores for the SA participants. The incident of SA happened between the ages of 9 and 17 [between the ages of 9-10 N=3 (5.3%), 11-12 N=8 (14%), 13-14 N=20 (35.1%), 15-16 N=22 (38.6%) and N=4 at the age of 17 (7%)]. Average time from the incident to the initiation of the psychiatric evaluation was 20.1±14.8 months. At the time of evaluation, 21 participants of 57 SA participants (44.3%) had at least one diagnosis; 17 had depression (29.8%), nine had depression and PTSD (15.8%), one had depression and ADHD, while three (5.3%) had subthreshold depressive symptoms. Although 14 participants used antidepressants previously, none of the participants were on any antidepressants in the last four weeks prior MRI scanning. Three SA participants (5.3%) reported occasional smoking, 5 preferred not to reply the question on substance abuse, while none of the controls reported a history of any drug abuse (Table 1).

The comparison of hippocampus and amygdala volumes between SA and HC groups

SA participants had larger right and left hippocampal volumes than the controls (Table- 2). Right amygdala volumes of the SA group were greater than the controls. Although the left amygdala volumes were larger in the abuse group, the difference did not reach a statistically significant level. We did not find any correlation of hippocampus or amygdala volumes and CTQ for sexual abuse or total CTQ scores.

The cortical thickness results

Inferior frontal gyrus (T=3.5, p<0.01, cluster size=694 mm2, x=51 y=-30 z=6) had smaller cortical thickness in the abused group when

TABLE 1. Demographic and clinical variables of sexually abused and non-abused groups.

Variables	*Sexually Abused Group (N=57) Mean ± SD*	*Non-abused Group (N=33) Mean ± SD*	*Comparison*
Age (years)	16.35 ± 1.11	17.6 ± 1.83	U=1043 p > 0.05
Education (years)	9.83 ± 1.47	10.67 ± 1.5	U=1044 p > 0.05
SES	28.6 ± 6.1	39.3 ± 5.9	T=8 df=88 p < 0.001
CTQ Emotional Abuse	10.7±5.6	5.5±1.2	U=250 p<0.001
CTQ Physical Abuse	7.9±4.9	5±0	U=511 p<0.001
CTQ Physical Neglect	8.2±3.4	5.6±1.6	U=459 p<0.001
CTQ Emotional Neglect	12±6.5	7.8±4.2	U=572 p<0.001
CTQ Total	53.7±21.5	29±5.1	U=168 p<0.001
CTQ Sexual Abuse	14.8±7.3	5±2	U=184 p<0.001
BDI Scores	21.2 ± 17.3	4.75 ± 4.57	U=414 p < 0.001
STAI 1 Scores	46.3±14.8	31.6±7.7	U=414 p<0.001
STAI 2 Scores	49.9±13.6	38.7±6.5	U=404 p<0.001
IQ Scores	82.1 ± 16.3	100.3 ± 10.1	T=5.7 df=88 p < 0.001

BDI: Beck Depression Inventory CTQ: Childhood Trauma Questionnaire IQ: Intelligence Quotient SES: Socio-Economic Situation STAI: State-Trait Anxiety Inventory

TABLE 2. The comparison of hippocampus and amygdala volumes between sexually abused and non-abused groups.

Volume	*Sexually Abused group (N=57) Mean ± SD*	*Non-abused group (N=33) Mean ± SD*	*F-value*	*p-value*
L Amygdala	1602.39±178.29	1549.89±152.29	3.62	*p*=0.06
R Amygdala	1746.93±189.72	1692.44±149.3	6.54	*p* < .05
L Hippocampus	4033.47±364.86	3923.56±336.66	8.45	*p* < .05
R Hippocampus	4208.29±379.90	4117.72±330.65	5.68	*p* < .05

L: Left R: Right

compared with controls (Figure 2). No correlation was detected between CTQ sexual abuse or total trauma scores with any PFC region thickness. Age and CT or IQ and CT were also not related.

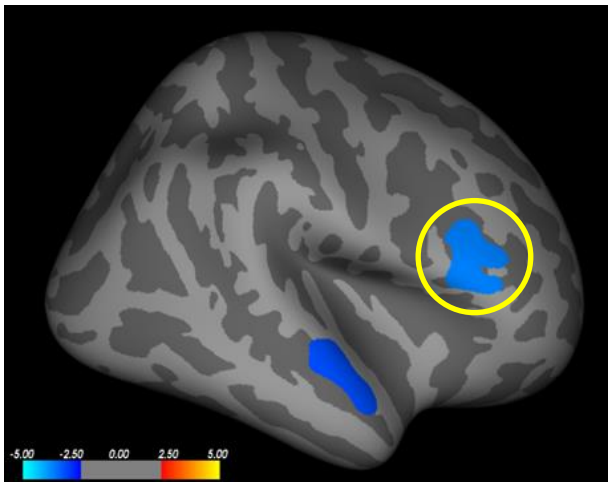

FIGURE 2. Cortical thickness comparison between sexually abused group and non-abused group. The sexually abused group have reduced cortical thickness in the right inferior frontal gyrus (T=3.5 , p<0.01, cluster size=694 mm2, x=51 y=-30 z=6; depicted in the yellow circle) when compared with non-abused group.

Discussion

In this study we found that hippocampus and amygdala volumes were larger and right inferior frontal gyrus cortex was thinner in a group of adolescents with SA history when compared with HCs. Although the structural differences were apparent between groups, none of the structural findings were correlated with total or sexual abuse CTQ scores. All of the research participants had well documented SA history but only some of them had psychiatric diagnosis. Moreover, the SA scores were above the cut-off value only in the abused group. These aspects of our data suggest that our findings are related only with SA and but not with the other abuse types or psychiatric diagnoses.

The harmful effects of CAEs are accepted widely. Earlier research focused on its effects on cognition and emotion processing. In recent years, the views on the effects of CAEs on a developing brain have changed and possible adaptation mechanisms to trauma are now being considered (36). In an unpredictable environment, the delay of gratification may result with the loss of assets and trust in other people may lead to vulnerability; accordingly, impulsive and hypervigilant behaviors would be adaptive (36). The latent vulnerability theory by McCrory and Viding propose that the modification of brain structure and function allows the adjustment of the reaction to a threatening environment (11). Although this adaptation has its perks it also has the risk of future medical and psychiatric problems (13,17).

Limbic cortex volumetric measurements are not consistent between children and adults who have CAE history. The majority of studies found that the adults with CAEs have smaller amygdala and hippocampus volumes (4,5,8). Nonetheless, the larger part of studies with abused children revealed larger limbic cortical volumes when compared with non-abused children (6,7,37–39). If the developmental trajectory of the limbic cortex and adaptation to a dangerous environment are considered this discordance can be resolved. Hippocampus and amygdala volumes follow an inverted U-shape through healthy childhood and reaches peak volume at the end of the adolescence; at the age of 17.3 and 19.7 respectively (40). Callaghan and Tottenham suggested that the rapid maturation of brain regions related to emotion networks, such as hippocampus and amygdala may allow to process threats more effectively (10). It is well known that children with CAEs have a tendency to detect dangerous stimuli and have a hyperactive amygdala (9,26) The overall picture suggests that children with CAEs have an abnormal development of the limbic cortex but do not have smaller hippocampus or amygdala.

The changes in PFC regions as a consequence of CAEs may also be adaptive in a perilous environment. Since a decrease in cortical thickness is viewed as an optimization of the computation in frequently utilized circuits (14), increased computational speed between IFG and limbic cortex may subserve the survival mechanism. On the other hand, the loss of the "brake" activity of the right IFG on impulsivity may cause loss of self-control and lead to externalization problems as shown by Barch et al. (13). Supporting this view, previous studies found smaller volumes (16–19) or thinning (6,22,23,43,24,25,44) of PFC in children with CAEs. Furthermore, several studies specifically reported reduced cortical thickness of the right IFG in children with CAEs (17,22,24). Findings of a very recent study suggest that thinner IFG may be a biomarker of maltreatment as it is seen in PTSD (post-traumatic stress disorder) children with maltreatment but not in PTSD children without maltreatment history. Interestingly, we found the same neural marker in the children with SA history. We suggest that larger amygdala and hippocampus with thinner IFG represents structural evidence for a hyperactive threat evaluation, orientation and response system in children with SA history. This hyperactive system allows the child to orient and respond to immediate threats but causes the child to be hypervigilant and impulsive and hence, predispose the victim to future behavioral problems. Although

focusing only on female individuals may pose a limitation, we decided to include only females to have a homogenous population excluding the gender effects on a developing brain which may be affected by dissimilar sex hormone levels.

The IQ discrepancy between groups in our study may be seen as a limitation. The SA group has lower IQ than control participants, which is also a finding that is observed in prior studies. Lower IQ of the abused group may be a developmental consequence of CAEs or a vulnerability factor for abuse. However, there's a possibility that the IQ test results of the abused group are misleading. Frankenhuis and deWeert postulated that when the children are evaluated in threatening conditions, abused group may outperform the non-abused group who are reared in a safe environment and the non-abused group would do the opposite in test conditions (36). Therefore, lower IQ detected in abused girls may not be a limitation but rather a failure to demonstrate normal IQ values that cannot be grasped by standard measurements. On the other hand, the discrepancy of SES between groups in our study is a limitation that may have implications on findings as it is known that poverty in childhood has detrimental effects on the structure and function of prefrontal and limbic cortices (46).

The difference of the selection of SA cases and HC also produce a limitation as the SA cases are directed from by judicial system and HC are enrolled from schools. It would be interesting to see the difference between the HC and SA children not directed by the judicial system but enrolled from schools as they would probably have similar SES and IQ levels. Moreover, schoolchildren with SA history may also have a more stable environment than the children directed by the judicial system. Of note, 77.2% of the SA children were perpetrated by non-relatives. This finding raises the possibility that SA cases in the general population may be overlooked as the public prosecutors were not informed. Therefore, the comparison of SA cases recruited from judicial system and HC from schools may be flawed. On the other hand, it would be almost impossible to find cases which were not reported in a school setting, as not reporting a SA is a serious crime. Therefore, we assume that most of the SA cases in the general population are not reported.

We conducted the research in a group of children heterogenous in diagnostic status. We must note that we enrolled children who were free from psychotropic medications for four weeks before the evaluation to minimize the effects of antidepressants on neurogenesis. However, we did not have a group that is large enough to conduct a statistical analysis with adequate power to dissect the effects of the clinical variables. We believe that our study reflects the brain changes of SA victims in general population. Moreover, SA scores were above the cut-off value only in the research group. Therefore, we suggest that our findings are related only to SA. This aspect of our findings shows us that SA cases that do not have a diagnosis must not be overlooked. Yet, caution is advised while extrapolating our results to maltreated groups homogeneous in diagnostic status. Furthermore, the lack of a clinical or a non-abuse trauma comparison group of adolescents yields another limitation. One must also consider that the mental health problems exist on a continuum, therefore the results do not rule out that the findings could be related to mental health problems.

All SA children were safe from their perpetrators and most of the SA children were living with their family or close relatives from the start of the judiciary process. Since more than the two thirds of the SA group had one or two incidents, we deduced that most of the children were not living under a constant threat as the incident led to the rapid prosecution of the perpetrator. Moreover, 19.3 % of the cases had SA before the age of 13 and a great majority the children were abused by non-relatives. Regarding the data, we assumed that most of the cases were living in a relatively safe environment following the incident and the early childhood SA is not the case for the majority of the SA group. Therefore, we can assume that the neurobiological difference between the SA group and the HC may be attributed to SA itself. However, we cannot rule out the effects of a persistent threat or the effects of an early SA gone unreported. The size of the subgroups precludes us to perform further statistical analysis.

We did not directly test whether there is a computational power increase by cortical thinning of IFG. However, the presence of healthy children in our SA group suggests that the possibility of an adaptive process is high. Based on the indirect evidence presented in this study structural and functional connectivity of IFG with limbic structures in SA victims should be tested in future research. In addition to our findings in the PFC we found cortical thickness differences between groups in separate brain regions, however, since our hypothesis was based on PFC and limbic cortex, we did not present those findings. Interested readers may find those cortical difference results in the supplementary material.

We detected structural differences in children with SA when compared with non-SA group. Larger amygdala and hippocampus volumes accompanied by thinner IFG suggest that there is a hyperactive threat evaluation, orientation and response system. We propose that these changes may help the child to adapt to an ill-environment in the short term while making the child susceptible to future psychiatric

problems or externalization (13,17). Our findings will help to gain insight into the structural brain changes in abused children who seem healthy. Considering these changes will increase our empathy to these adolescents; help to minimize the stigma on abused children who have impulsive behaviors and foster clinicians to follow up healthy children who have sexual abuse history. Revealing the neural underpinnings of the consequences of SA may also serve to find a way for psychological rehabilitation (45). We suggest abused but otherwise healthy children should be considered for psychological interventions as the normal trajectory of limbic cortical development continues up to the end of the second decade. Future studies investigating the hypothesis of brain structural adaptation to trauma are needed.

Ethics approval

The study was approved by the local ethical review board of Ege University School of Medicine (12-1.1/63) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflicts of interest

None of the authors have biomedical financial interests or potential conflicts of interest.

References

1. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998 May;14(4):245–58.

2. Nikolaidis G, Petroulaki K, Zarokosta F, Tsirigoti A, Hazizaj A, Cenko E, et al. Lifetime and past-year prevalence of children's exposure to violence in 9 Balkan countries: the BECAN study. Child Adolesc Psychiatry Ment Health. 2018;12:1.

3. Chen LP, Murad MH, Paras ML, Colbenson KM, Sattler AL, Goranson EN, et al. Sexual abuse and lifetime diagnosis of psychiatric disorders: systematic review and meta-analysis. Mayo Clin Proc. 2010 Jul;85(7):618–29.

4. Ahmed-Leitao F, Spies G, van den Heuvel L, Seedat S. Hippocampal and amygdala volumes in adults with posttraumatic stress disorder secondary to childhood abuse or maltreatment: A systematic review. Psychiatry Res Neuroimaging. 2016 Oct 30;256:33–43.

5. Calem M, Bromis K, McGuire P, Morgan C, Kempton MJ. Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples. NeuroImage Clin. 2017;

6. Whittle S, Dennison M, Vijayakumar N, Simmons JG, Yücel M, Lubman DI, et al. Childhood maltreatment and psychopathology affect brain development during adolescence. J Am Acad Child Adolesc Psychiatry. 2013;52(9).

7. Whittle S, Simmons JG, Hendriksma S, Vijayakumar N, Byrne ML, Dennison M, et al. Childhood maltreatment, psychopathology, and the development of hippocampal subregions during adolescence. Brain Behav. 2017;7(2):e00607.

8. Paquola C, Bennett MR, Lagopoulos J. Understanding heterogeneity in grey matter research of adults with childhood maltreatment—A meta-analysis and review. Neurosci Biobehav Rev. 2016;69:299–312.

9. Ganzel BL, Kim P, Gilmore H, Tottenham N, Temple E. Stress and the healthy adolescent brain: evidence for the neural embedding of life events. Dev Psychopathol. 2013 Nov;25(4 Pt 1):879–89.

10. Callaghan BL, Tottenham N. The Stress Acceleration Hypothesis: Effects of early-life adversity on emotion circuits and behavior. Curr Opin Behav Sci. 2016 Feb;7:76–81.

11. McCrory EJ, Viding E. The theory of latent vulnerability: Reconceptualizing the link between childhood maltreatment and psychiatric disorder. Dev Psychopathol. 2015 May;27(2):493–505.

12. Miller GE, Chen E, Parker KJ. Psychological Stress in Childhood and Susceptibility to the Chronic Diseases of Aging: Moving Towards a Model of Behavioral and Biological Mechanisms. Psychol Bull. 2011 Nov;137(6):959–97.

13. Barch DM, Belden AC, Tillman R, Whalen D, Luby JL. Early Childhood Adverse Experiences, Inferior Frontal Gyrus Connectivity, and the Trajectory of Externalizing Psychopathology. J Am Acad Child Adolesc Psychiatry. 2018;57(3):183–90.

14. Sowell ER, Thompson PM, Toga AW. Mapping Adolescent Brain Maturation Using Structural Magnetic Resonance Imaging [Internet]. Adolescent Psychopathology and the Developing Brain. Oxford University Press; 2007 [cited 2020 Dec 24]. Available from: https://oxford.universitypressscholarship.com/view/10.1093/acprof:oso/9780195306255.001.0001/acprof-9780195306255-chapter-3

15. Carrion VG, Weems CF, Eliez S, Patwardhan A, Brown W, Ray RD, et al. Attenuation of frontal asymmetry in pediatric posttraumatic stress disorder. Biol Psychiatry. 2001 Dec 15;50(12):943–51.

16. Hanson JL, Chung MK, Avants BB, Shirtcliff EA, Gee JC, Davidson RJ, et al. Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. J Neurosci Off J Soc Neurosci. 2010 Jun 2;30(22):7466–72.

17. Luby JL, Barch D, Whalen D, Tillman R, Belden A. Association Between Early Life Adversity and Risk for Poor Emotional and Physical Health in Adolescence: A Putative Mechanistic Neurodevelopmental Pathway. JAMA Pediatr. 2017 Dec 1;171(12):1168–75.

18. De Brito SA, Viding E, Sebastian CL, Kelly PA, Mechelli A, Maris H, et al. Reduced orbitofrontal and temporal grey matter in a community sample of maltreated children. J Child Psychol Psychiatry. 2013 Jan;54(1):105–12.

19. Kelly PA, Viding E, Puetz VB, Palmer AL, Mechelli A, Pingault J-B, et al. Sex differences in socioemotional functioning, attentional bias, and gray matter volume in maltreated children: A multilevel investigation. Dev Psychopathol. 2015 Nov;27(4 Pt 2):1591–609.

20. Walsh ND, Dalgleish T, Lombardo MV, Dunn VJ, Van Harmelen A-L, Ban M, et al. General and specific effects of early-life psychosocial adversities on adolescent grey matter volume. NeuroImage Clin. 2014;4:308–18.

21. Hutton C, Draganski B, Ashburner J, Weiskopf N. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. NeuroImage. 2009 Nov 1;48(2):371–80.

22. Kelly PA, Viding E, Wallace GL, Schaer M, De Brito SA, Robustelli B, et al. Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: Neural markers of vulnerability? Biol Psychiatry. 2013;

23. Gold AL, Sheridan MA, Peverill M, Busso DS, Lambert HK, Alves S, et al. Childhood abuse and reduced cortical thickness in brain regions involved in emotional processing. J Child Psychol Psychiatry. 2016;57(10).

24. Busso DS, McLaughlin KA, Brueck S, Peverill M, Gold AL, Sheridan MA. Child Abuse, Neural Structure, and Adolescent Psychopathology: A Longitudinal Study. J Am Acad Child Adolesc Psychiatry. 2017;56(4):321-328.e1.

25. Lim L, Hart H, Mehta M, Worker A, Simmons A, Mirza K, et al. Grey matter volume and thickness abnormalities in young people with a history of childhood abuse. Psychol Med. 2018;48(6):1034–46.

26. McLaughlin KA, Peverill M, Gold AL, Alves S, Sheridan MA. Child Maltreatment and Neural Systems Underlying Emotion Regulation. J Am Acad Child Adolesc Psychiatry. 2015 Sep 1;54(9):753–62.

27. Mesulam M-M, editor. Principles of Behavioral and Cognitive Neurology. 2 edition. Oxford ; New York: Oxford University Press; 2000. 574 p.

28. Gokler B. Reliability and validity of schedule for affective disorders and Schizophrenia for school age children-present and lifetime version-Turkish version (K-SADS-PL-T)[in Turkish]. Turk J Child Adolesc Ment Health. 2004;11:109–16.

29. Hisli N. A study on the validity of the Beck Depression Inventory. Turk Psychol J. 1998;6:118–23.

30. Öner N, LeCompte WA. Durumluk-sürekli kaygı envanteri el kitabı. Boğaziçi Üniversitesi Yayınları; 1985.

31. Sar V, Ozturk E, Ikikardes E. Validity and reliability of the Turkish version of Childhood Trauma Questionnaire. Turk Klin Tip Bilim Derg. 2012;32(4):1054–63.

32. Savaşır I, Şahin N. Wechsler çocuklar için zeka ölçeği (WISC-R) el kitabı. Türk Psikologlar Derneği Yayın Ank. 1995;

33. Sezgin N,Baştug G,Karaagac SY, Yilmaz B. Wechsler Yetişkinler için Zeka Ölçeği gözden geçirilmiş formu (WAIS-R) Türkiye standardizasyonu: Ön çalışma. Ank Üniversitesi Dil Ve Tar-Coğrafya Fakültesi Derg. 2017;54(1).

34. Fischl B. FreeSurfer. Neuroimage. 2012;62(2):774–81.

35. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002;33(3):341–55.

36. Does Early-Life Exposure to Stress Shape or Impair Cognition? - Willem E. Frankenhuis, Carolina de Weerth, 2013 [Internet]. [cited 2020 Dec 29]. Available from: https://journals.sagepub.com/doi/abs/10.1177/0963721413484324

37. Tupler LA, De Bellis MD. Segmented hippocampal volume in children and adolescents with posttraumatic stress disorder. Biol Psychiatry. 2006 Mar 15;59(6):523–9.

38. Tottenham N, Hare TA, Quinn BT, McCarry TW, Nurse M, Gilhooly T, et al. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. Dev Sci. 2010 Jan 1;13(1):46–61.

39. Paquola C, Bennett MR, Hatton SN, Hermens DF, Groote I, Lagopoulos J. Hippocampal development in youth with a history of childhood maltreatment. J Psychiatr Res. 2017 Aug;91:149–55.

40. Wierenga LM, Langen M, Oranje B, Durston S. Unique developmental trajectories of cortical thickness and surface area. NeuroImage. 2014 Feb 15;87:120–6.

41. Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, Williams SCR, et al. Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. J Child Psychol Psychiatry. 2009 Aug;50(8):943–51.

42. Lupien SJ, Parent S, Evans AC, Tremblay RE, Zelazo PD, Corbo V, et al. Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. Proc Natl Acad Sci. 2011;108(34):14324–9.

43. Kelly PA, Viding E, Puetz VB, Palmer AL, Samuel S, McCrory EJ. The sexually dimorphic impact of maltreatment on cortical thickness, surface area and gyrification. J Neural Transm Vienna Austria 1996. 2016 Sep;123(9):1069–83.

44. Bomyea J, Simmons AN, Shenton ME, Coleman MJ, Bouix S, Rathi Y, et al. Neurocognitive markers of childhood abuse in individuals with PTSD: Findings from the INTRuST Clinical Consortium. J Psychiatr Res. 2020;121:108–17.

45. Wierenga L, Langen M, Ambrosino S, van Dijk S, Oranje B, Durston S. Typical development of basal ganglia, hippocampus, amygdala and cerebellum from age 7 to 24. NeuroImage. 2014 Aug 1;96:67–72.

46. Taylor RL, Cooper SR, Jackson JJ, Barch DM. Assessment of Neighborhood Poverty, Cognitive Function, and Prefrontal and Hippocampal Volumes in Children. JAMA Netw Open [Internet]. 2020 Nov 3 [cited 2021 Mar 2];3(11). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7610187/