PLOS | ONE

RESEARCH ARTICLE

Altered Hemodynamic Activity in Conduct Disorder: A Resting-State fMRI Investigation

Jiansong Zhou[1]*, Nailin Yao[2], Graeme Fairchild[3], Yingdong Zhang[1], Xiaoping Wang[1]*

1 Mental Health Institute of The Second Xiangya Hospital, Central South University; Hunan Province Technology Institute of Psychiatry; Key Laboratory of Psychiatry and Mental Health of Hunan Province, Changsha, China, **2** Department of Psychiatry, The University of Hong Kong, Hong Kong, China, **3** Academic Unit of Psychology, University of Southampton, Southampton, United Kingdom

* xyjw6@aliyun.com (XW); zhoujs2003@aliyun.com (JZ)

Citation: Zhou J, Yao N, Fairchild G, Zhang Y, Wang X (2015) Altered Hemodynamic Activity in Conduct Disorder: A Resting-State fMRI Investigation. PLoS ONE 10(3): e0122750. doi:10.1371/journal.pone.0122750

Academic Editor: Wang Zhan, University of Maryland, College Park, UNITED STATES

Received: September 26, 2014

Accepted: February 13, 2015

Published: March 27, 2015

Data Availability Statement: All relevant data are within the paper.

Funding: This work was supported by Key Projects in the National Science & Technology Pillar Program during the Twelfth Five-Year Plan Period (2012BAK16B00), MOE (Ministry of Education in China) Project of Humanities and Social Sciences (Project No. 13YJC190033), the National Natural Science Foundation of China (NSFC, 30800368, 81371500), and the Science and Technology Committee of Shanghai Municipality for Shanghai Key Lab of Forensic Medicine (12DZ2271500: KF1006). The funders had no role in study design,

Abstract

Background

Youth with conduct disorder (CD) not only inflict serious physical and psychological harm on others, but are also at greatly increased risk of sustaining injuries, developing depression or substance abuse, and engaging in criminal behaviors. The underlying neurobiological basis of CD remains unclear.

Objective

The present study investigated whether participants with CD have altered hemodynamic activity under resting-state conditions.

Methods

Eighteen medication-naïve boys with CD and 18 age- and sex- matched typically developing (TD) controls underwent functional magnetic resonance imaging (MRI) scans in the resting state. The amplitude of low-frequency fluctuations (ALFF) was measured and compared between the CD and TD groups.

Results

Compared with the TD participants, the CD participants showed lower ALFF in the bilateral amygdala/parahippocampus, right lingual gyrus, left cuneus and right insula. Higher ALFF was observed in the right fusiform gyrus and right thalamus in the CD participants compared to the TD group.

Conclusions

Youth with CD displayed widespread functional abnormalities in emotion-related and visual cortical regions in the resting state. These results suggest that deficits in the intrinsic activity of resting state networks may contribute to the etiology of CD.

data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Introduction

Conduct disorder (CD) is characterized by a persistent pattern of antisocial behavior and aggression in childhood and adolescence [1]. Youth with CD not only inflict serious physical and psychological harm on others, but are at increased risk of sustaining personal injuries, as well as developing depression or substance abuse, and participating in recurrent criminal behaviors in adulthood [2,3]. The underlying neurobiology of CD remains unclear but has attracted growing attention in recent years [4].

Adolescents with CD showed reduced gray matter volume (GMV) in diverse cortical regions when compared to typically-developing (TD) comparison subjects in previous studies [5,6]. In addition, reduced neural responses have also been reported in diverse areas including the amygdala, anterior cingulate cortex, insula, and orbitofrontal cortex in youth with CD compared to TD controls [7–10]. Although most of these functional magnetic resonance imaging (fMRI) studies reported alterations in emotion- and cognition-related cortical and subcortical areas in CD [8], the direction of the effects differed between studies. For example, Sterzer et al. (2005) found reduced amygdala responses to negative pictures in adolescents with CD [11] whereas Herpertz et al. (2008) reported increased amygdala responses to negative pictures in CD [12]. This discrepancy in fMRI findings could be due to differences in task design across the studies. For this reason, an investigation of brain activity under baseline conditions in adolescents with CD would be informative and could have clinical and prognostic value.

Spontaneous low-frequency (<0.08 Hz) fluctuations of the blood oxygen level-dependent (BOLD) signal in the brain (as measured using resting-state functional magnetic resonance imaging, rs-fMRI) [13] have been shown to be closely related to spontaneous neuronal activity [14,15]. These fluctuations are believed to reflect baseline activity that is largely unrelated to cognitive activity [16]. A method that involves assessing amplitude of low-frequency fluctuations (ALFF) has recently been developed by Zang et al. [17] to measure whole-brain resting-state (rs)-fMRI. ALFF has been linked to neuronal glucose metabolism [18] and correlates with local field potential activity [19]. Alterations in ALFF have described in a number of disorders including schizophrenia and major depressive disorder [20,21], making the patterns of ALFF alterations potentially useful biomarkers for complex neuropsychiatric conditions. Therefore, this method could be used to assess the activity of intrinsic brain networks in patients with CD to examine whether they show abnormalities in resting state activity.

CD is characterized by deficits in guilt and empathy, impaired recognition of emotions [22–24], and impulsive, risky decision-making [22,25]. As these traits have been linked to emotion regulation centers such as the amygdala, insula, and anterior cingulate cortex (ACC) [26–30], and given previous evidence for changes in task-related activity in these regions [7–12], we hypothesized that participants with CD would show altered ALFF in these regions. If this hypothesis was supported, this might help to explain why CD is associated with deficits in emotion processing and decision-making.

A significant methodological advantage of our study is that we deliberately recruited a pure CD group by excluding participants who had comorbid attention-deficit/hyperactivity disorder (ADHD) or substance use disorders, which might account for some of the discrepancies in the results of previous studies of CD [31], although these confounding effects have been statistically controlled for in some studies [32–34]. Thus, studying a more homogenous sample of CD patients could elucidate the specific neurobiological factors underlying this developmental disorder. Finally, given that there are sex differences in the prevalence and developmental course of CD [35–38], this study focused on young male subjects only.

Methods and Materials

Participants

Thirty-six boys participated in this study, 18 with a DSM-IV diagnosis of CD and 18 age-matched typically-developing (TD) controls. All subjects were right-handed, and aged between 15 and 17 years. Participants with CD were recruited from the Hunan province Youth Detention Centre (YDC) in the People's Republic of China, whereas the participants in the TD group were recruited from schools in the community of Changsha, Hunan province. Information sheets describing the aims, content, and duration of the study were given to all the participants and parents, and all participants and parents provided written informed consent. This study was approved by the Biomedical Ethics Board of the second Xiangya Hospital, Central South University, People's Republic of China (S20080082).

Current and lifetime psychiatric problems were assessed in both CD and TD subjects by an experienced child psychiatrist using the Chinese version of the Schedule for Affective Disorder and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL) [39–41]. This is a semi-structured psychiatric interview based on DSM-IV criteria (American Psychiatric Association, 1994). The K-SADS-PL includes: 1) an unstructured Introductory Interview; 2) a Diagnostic Screening Interview; 3) the Supplement Completion Checklist; 4) the appropriate Diagnostic Supplements; 5) the Summary Lifetime Diagnoses Checklist; and 6) the Children's Global Assessment Scale (C-GAS) ratings. Participants with a history of neurological disorders including paralysis, loss of sensation, muscular weakness, epilepsy, seizures, chronic pain, confusion, and prolonged loss of consciousness due to head injury were excluded from the study. The majority of the items are scored using a 0–3 point rating scale (0: no information is available, 1: the symptom is not present, 2: subthreshold levels of symptomatology, and 3: threshold criteria). Any participants meeting the K-SADS-PL criteria for any other current or lifetime psychiatric disorder except CD, such as ADHD, mood disorder, anxiety disorder, mental retardation, or substance abuse or dependence were also excluded from the study.

Psychological assessment

The self-report questionnaire Screen for Child Anxiety Related Emotional Disorders (SCARED) [42] was used to assess anxiety disorder symptoms. The Birleson Depression Self-Rating Scale (DSRS) was used to assess depressive symptoms experienced during the preceding week [43]. Further details regarding the SCARED and DSRS questionnaires were reported in our previous articles [44,45].

MRI data acquisition

MRI data were obtained with a 3-Tesla scanner (Siemens Allegra; based at the Magnetic Resonance Center of Hunan Provincial People's Hospital, People's Republic of China) using an 8-channel phased-array head coil with participants lying in a supine position. Blood oxygen level-dependent (BOLD) functional MRI data were acquired using a gradient-echo echo-planar imaging (EPI) sequence [46,47]. Acquisition parameters were as follows: repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle = 90°, 100 volumes, 36 contiguous axial slices, anterior-posterior acquisition, in-plane resolution = 3.75 × 3.75 × 3.75 mm, slice thickness = 3mm, and field of view = 256×256mm. The overall acquisition time was = 6 minutes and 36 seconds. Slice acquisition order was contiguous. To reduce scanner noise and head motion, a foam pillow, extendable padded head clamps, and ear plugs were used when participants were in the scanner. Participants were asked to simply rest in the scanner remaining awake and alert, with their eyes closed and to stay as still as possible during the resting state

scan. Three-dimensional T1-weighted anatomical MRI data were acquired with a fast field echo sequence (Magnetization Prepared Rapid Gradient Echo, MPRAGE), using the parameters TR = 2000ms, TE = 3.36 ms, flip angle = 9°, 1 × 1 × 1mm voxels, FOV = 256×256mm, number of slices = 144.

Functional data analysis

Image preprocessing of resting state fMRI data. Preprocessing of resting state fMRI data was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) software. The first 10 volumes were discarded for each individual to allow for the effects of magnetic saturation. All functional images were corrected for slice timing and head movement. All 36 participants remained within < 2 mm of displacement in any direction and within 2 degrees of rotation in any direction, so none of the data were excluded from further analysis due to excessive head movement. Prior to band-pass filtering (0.01 ~ 0.08Hz) which controls for the physiological "noise" (cardiac and respiratory-related artifacts), the following nuisance covariates were regressed from the BOLD signal [48]: 6 rigid-body parameters, white matter signal, and cerebrospinal fluid (CSF) signal. After band-pass filtering, all functional data were normalized to the Montreal Neurological Institute (MNI) space by applying the transformation parameters obtained from the structural images (see the following "structural image analysis" section for details) and smoothed (4 mm full width at half maximum (FWHM) Gaussian kernel).

ALFF calculations. ALFF calculations were performed using REST software version 1.8 (www.restfmri.net) [49]. First, for each voxel of the brain, the BOLD time series was converted to the frequency domain using a Fast Fourier Transform. The square root of the power spectrum was then calculated and averaged across a specified frequency range (0.01–0.08Hz) to eliminate remaining low- and high-frequency noise in the resting state data [13,50]. This value was then transformed using Fisher's Z and is referred to as the ALFF for a given voxel [17].

Structural image analysis. Individual structural T1-weighted images were co-registered to the mean motion-corrected functional images using a linear transformation. They were then segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) in MNI space by using "New Segment" in SPM8. The DARTEL procedure [21] was then used to create a study-specific template. GM, WM and CSF were then normalized to MNI space and smoothed with an 8 mm FWHM Gaussian kernel. Mean modulated and smoothed GM maps (intensity threshold = 0.2) were used to generate a group GM mask and applied as a mask for analyzing ALFF differences in the comparisons, specific to the groups included in a particular test.

Statistical analysis

Demographic factors were compared using independent two-sample t-tests using the Statistical Package for Social Sciences (version 15.0.1) (SPSS for Windows, 2006) [51]. Between-group voxel-wise comparisons were performed using non-parametric permutation tests (5000 permutation) implemented in RANDOMISE [52] in FSL. Statistical comparisons between groups in terms of ALFF were restricted to regions within the corresponding GM mask generated as described above. The voxel-based statistical tests were corrected for multiple comparisons at a significance level of $p<0.05$ using Monte Carlo simulations (uncorrected single voxel significance level of $p<0.001$ and a minimum cluster size based on the size of the gray matter mask) [53,54]. The relationship between the number of CD symptoms in the K-SADS-PL and ALFF was assessed within the CD group using Pearson's correlations.

Table 1. Demographic characteristics and descriptive statistics for the CD and TD.

	CD (*n* = 18)		TD (*n* = 18)			*df*	*p*
	n	%	*n*	%	χ^2		
Parental marital status (divorced)	4	22.2	1	5.6	2.1	1	0.15
Family income (monthly)[a]					1.8	3	0.62
<1000	5	27.8	2	11.1			
1000–1999	7	38.8	8	44.5			
2000–3499	5	27.8	6	33.3			
>3500	1	5.6	2	11.1			
	mean	*sd*	*mean*	*sd*	*t*		
Age (years)	16.1	0.5	15.9	0.3	1.1	34	0.27
Duration of education (years)	9.4	2.0	9.2	1.9	0.7	34	0.47
Father's duration of education (years)	8.8	2.6	10.4	2.2	1.9	34	0.07
Mother's duration of education (years)	8.2	4.1	10.1	3.5	1.6	34	0.13
K-SADS-PL							
Positive items of CD	7.4	2.1	0.0	0.0	14.8	34	<0.001
Total symptoms Score of CD	31.6	4.1	15.7	0.7	16.1	34	<0.001
SCARED	16.1	7.4	17.4	10.4	0.4	32	0.67
DSRS	11.8	3.8	9.8	4.1	1.6	34	0.12

SCARED = Screen for Child Anxiety Related Emotional Disorders; DSRS = Birleson Depression Self-Rating Scale. K-SADS-PL: the Schedule for Affective Disorder and Schizophrenia for School-Age Children-Present and Lifetime.

[a] Chinese RMB (yuan) minimum monthly salary (per person).

doi:10.1371/journal.pone.0122750.t001

Results

Demographic and clinical characteristics

The CD and TD groups were matched in terms of age, education level, parental education levels, parental marital status, family income, and levels of self-reported anxiety and depression (Table 1).

Group differences in resting state activity

As shown in the Fig 1 and in Table 2, compared with the TD participants, the CD participants showed decreased ALFF in the bilateral amygdala/parahippocampus, right lingual gyrus, left cuneus and right insula. In contrast, the CD participants showed increased ALFF in the right fusiform gyrus, and right thalamus relative to the TD participants. There was no significant correlation between the number of CD symptoms and ALFF results in the CD group.

Difference maps at the given threshold, corrected for multiple comparisons (Monte-Carlo Simulation, cluster size = 162 mm^3 (6 voxels), $T > 3.6$ (or $T < -3.6$), and $p < 0.001$, uncorrected). Green indicates regions where participants with CD had lower ALFF when compared with TD participants, while red indicate regions the converse. The column bars show average ALFF z scores (±standard error) of the clusters (as listed orderly in Table) with significantdifference between TD and CD groups.

Discussion

The current study is, to our knowledge, the first to identify functional hemodynamic changes in boys with CD relative to typically-developing controls during the resting state. The results

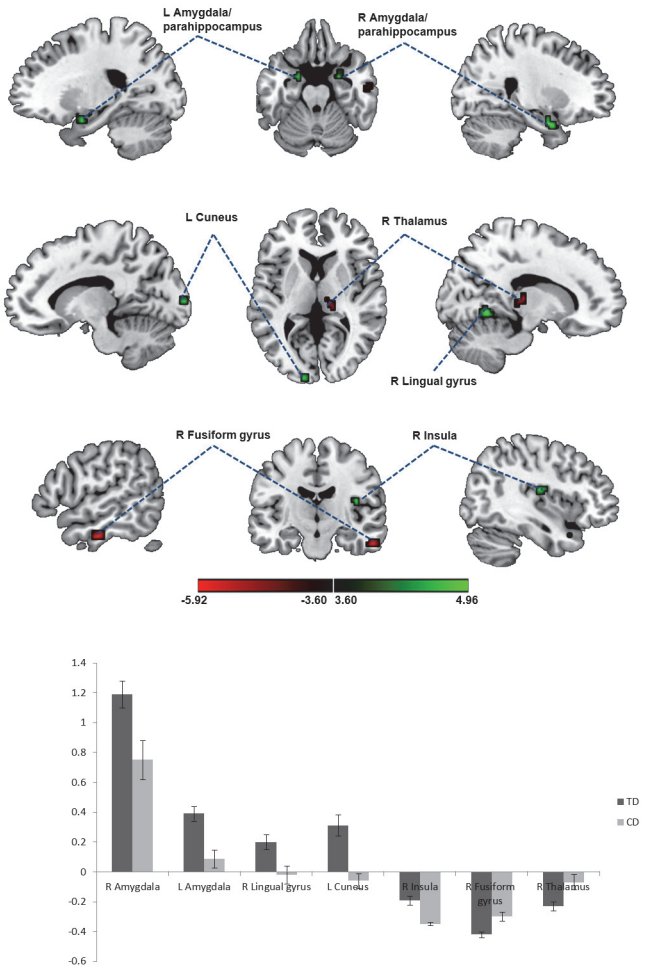

Fig 1. ALFF result in participants with CD compared to TD participants.

doi:10.1371/journal.pone.0122750.g001

Table 2. The significant differences ALFF brain areas between CD and TD groups.

Direction of difference	Number of voxels	x	y	z	Side	Brain regions	BA	T-value
Lower in CD	18	25	2	-25	R	amygdala/parahippocampus	28	4.96
	7	-20	-1	-22	L	Amygdala/parahippocampus	n/a	4.94
	14	13	-58	-4	R	Lingual gyrus	19	4.81
	6	-11	-100	5	L	Cuneus	n/a	4.22
	6	40	-16	17	R	Insula	13	4.59
Greater in CD	16	58	-10	-28	R	Fusiform gyrus	20	-5.92
	9	13	-22	8	R	Thalamus	n/a	-4.58

Group ALFF differences are shown at $p < 0.001$ of multiple comparison correction (cluster size = 162 mm3, $T > 3.6$ (or $T < -3.6$)). x, y, z: coordinates in the MNI atlas extending from z = -65 mm to +80 mm. T values are from a t-test of the peak voxel (showing greatest statistical difference within a cluster); a negative T value means greater ALFF in the CD group. Both age and education were regressed from the data as nuisance covariates.
BA: Brodmann area. L, R: left and right.

doi:10.1371/journal.pone.0122750.t002

support the hypothesis that emotion-related areas including the amygdala and insula would show altered hemodynamic fluctuations in participants with CD. The findings also revealed group differences in visual regions such as the left cuneus, right lingual gyrus and right fusiform gyrus, although increased ALFF was observed in the latter region in participants with CD relative to TD controls

The amygdala and insula are strongly implicated in emotion processing [55], previous studies reported reduced gray matter volume in the amygdala and insula [5], and reduced amygdala activation in affective tasks in male adolescents with CD [55]. This study is the first to observe decreased ALFF was revealed in CD compared to TD participants. As ALFF measures the synchronicity of neuronal activity signals among remote regions of the brain, and the ALFF signal has been shown to reflect regional spontaneous neuronal activity, the lower ALFF exhibited in the amygdala and insula in CD individuals might reflect decreased energy consumption in these regions [18]. The insula [56], amygdala, and regions in the prefrontal cortex such as the orbitofrontal cortex [57] have been identified as critical structures for emotion processing, motivation, decision-making [28,58–60], and are functionally linked to negative emotional responses [61,62] and arousal effects [63]. These results suggest that the abnormal spontaneous activity of the amygdala and insula may play a role in the underlying pathophysiology of children with CD [22,23,64].

Another interesting finding was that lower ALFF was observed in right lingual gyrus and left cuneus, whereas higher ALFF values were detected in right fusiform gyrus in CD compared to TD individuals. The cuneus is involved in basic aspects of visual processing [65]. The lingual gyrus is linked to visual processing, logical reasoning [66] and visual memory encoding [67]. Our finding of lower ALFF in lingual gyrus and cuneus is in line with previous studies showing decreased activation in lingual gyrus in women with borderline personality disorder [68]. Moreover, a recent study reported that activity in lingual gyrus and cuneus were negatively correlated with risk-taking in CD individuals [69]. The fusiform gyrus appears to be involved in facial identity processing, and plays an important role in facial expression perception [70]. Previous fMRI studies reported mixed findings in terms of the activity of the fusiform gyrus in CD [71–73] which might be due to differences between fMRI tasks in cognitive load or difficulty. Our study is the first to investigate hemodynamic functioning in adolescents with CD during the resting state, which is argued to be a better reflection of "baseline" function than task-related activity. We speculate that higher ALFF in fusiform gyrus implies greater spontaneous neuronal activity at rest [18] possibly leaving less 'reserve' for the demands of fMRI tasks involving emotion processing. This hypothesis could be tested in future studies using alternative methods that provide measures of brain metabolic activity such as arterial spin-labelling [74].

Finally, the present study showed increased spontaneous neuronal activity in the thalamus of CD compared with TD participants. Altered functional activity was reported in previous fMRI studies. One study showed increased thalamus activity during the Stroop task in CD patients compared to TD controls [75], while another study showed that the thalamus was more active in violent offenders than non-offenders during a conflict-related task [76]. The thalamus is thought to play an important role in stress adaptation and controlling motor systems [76]. Therefore, it is presently unclear whether the abnormal spontaneous thalamic activity observed in the present study is related to deficits in emotion processing or cognitive control. Consequently, future studies could investigate the impact of abnormal thalamus activity on performance of emotional and cognitive tasks in CD participants.

Strength and limitations

To our knowledge, this is the first study to investigate baseline fluctuations in hemodynamic activity in individuals with CD. This pilot study will be helpful in terms of designing future studies investigating functional abnormalities in CD at the network level, based on the deficits exhibited by the present sample. These studies could use graph theoretical methods to explore patterns of connectivity during the resting state. It would also be interesting to investigate structure-function relationships within the same individuals to test whether structural changes (e.g. in gray matter volume or white-matter tract integrity) underpin the observed deficits in resting state activity.

An important limitation of the study is that, although the two groups did not differ in terms of years of education, IQ was not systematically measured or included as a covariate in the analyses. The CD group might have been expected to have lower IQs than the TD group [77], and it would have been optimal to control for this variable in the statistical analyses. Another limitation is that the participants recruited were all male adolescents, so it is not known whether these findings would generalize to females with CD or adults with antisocial personality disorder. Furthermore, the study did not use any instrument to assess personality traits associated with CD such as callous-unemotional (CU) traits [78]. Future resting state studies should assess personality traits such as CU traits to examine whether different subtypes of CD (i.e., those with limited prosocial emotions) or different symptom profiles map onto alterations in resting state fMRI activity. Finally, we note that the repetition time of the MRI sequence that we used is relatively long compared to other studies (3 s), which might introduce low-frequency noise to the resting-state signal. However, a low-pass filtering using a cut-off of 0.08 Hz was used in our study to control for the possible effects of physiological "noise" such as heart rate and respiration [79].

Conclusion

In summary, the current study provides evidence supporting the hypothesis that CD is associated with dysfunction in emotion-related cortical regions, including the insula and amygdala, and regions involved in face processing such as the fusiform gyrus, lingual gyrus and left cuneus. The key contribution of this study is to show that these abnormalities in brain activity are observed even under resting conditions, and therefore might reflect changes in intrinsic baseline activity in CD. These findings might help to explain why individuals with CD show difficulties in emotion recognition and decision-making. It is also possible that group differences in baseline activity might have influenced some of the findings of earlier fMRI studies comparing CD and TD individuals using emotion-related or cognitive tasks.

Acknowledgments

We thank the Magnetic Resonance Center of Hunan Provincial People's Hospital, for providing scanning time and technical assistance.

Author Contributions

Conceived and designed the experiments: JSZ XPW. Performed the experiments: JSZ YDZ. Analyzed the data: NLY JSZ. Contributed reagents/materials/analysis tools: NLY. Wrote the paper: JSZ NLY GF.

References

1. Barry CT, Frick PJ, DeShazo TM, McCoy MG, Ellis M, et al. The importance of callous-unemotional traits for extending the concept of psychopathy to children. J Abnorm Psychol. 2000; 109: 335–340. PMID: 10895572
2. Dadds MR, Fraser J, Frost A, Hawes DJ. Disentangling the underlying dimensions of psychopathy and conduct problems in childhood: a community study. J Consult Clin Psychol. 2005; 73: 400–410. PMID: 15982138
3. Lahey BB, Loeber R, Burke JD, Applegate B. Predicting future antisocial personality disorder in males from a clinical assessment in childhood. J Consult Clin Psychol. 2005; 73: 389–399. PMID: 15982137
4. van Goozen SH, Fairchild G, Snoek H, Harold GT. The evidence for a neurobiological model of childhood antisocial behavior. Psychol Bull. 2007; 133: 149–182. PMID: 17201574
5. Fairchild G, Passamonti L, Hurford G, Hagan CC, von dem Hagen EA, et al. Brain structure abnormalities in early-onset and adolescent-onset conduct disorder. Am J Psychiatry. 2011; 168: 624–633. doi: 10.1176/appi.ajp.2010.10081184 PMID: 21454920
6. Huebner T, Vloet TD, Marx I, Konrad K, Fink GR, et al. Morphometric brain abnormalities in boys with conduct disorder. J Am Acad Child Adolesc Psychiatry. 2008; 47: 540–547. doi: 10.1097/CHI.0b013e3181676545 PMID: 18356764
7. Jones AP, Laurens KR, Herba CM, Barker GJ, Viding E. Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. Am J Psychiatry. 2009; 166: 95–102. doi: 10.1176/appi.ajp.2008.07071050 PMID: 18923070
8. Marsh AA, Finger EC, Fowler KA, Adalio CJ, Jurkowitz IT, et al. Empathic responsiveness in amygdala and anterior cingulate cortex in youths with psychopathic traits. J Child Psychol Psychiatry. 2013; 54: 900–910. doi: 10.1111/jcpp.12063 PMID: 23488588
9. Rubia K, Halari R, Smith AB, Mohammad M, Scott S, et al. Shared and disorder-specific prefrontal abnormalities in boys with pure attention-deficit/hyperactivity disorder compared to boys with pure CD during interference inhibition and attention allocation. J Child Psychol Psychiatry. 2009; 50: 669–678. doi: 10.1111/j.1469-7610.2008.02022.x PMID: 19236528
10. Rubia K, Smith AB, Halari R, Matsukura F, Mohammad M, et al. Disorder-specific dissociation of orbitofrontal dysfunction in boys with pure conduct disorder during reward and ventrolateral prefrontal dysfunction in boys with pure ADHD during sustained attention. Am J Psychiatry. 2009; 166: 83–94. doi: 10.1176/appi.ajp.2008.08020212 PMID: 18829871
11. Sterzer P, Stadler C, Krebs A, Kleinschmidt A, Poustka F. Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. Biol Psychiatry. 2005; 57: 7–15. PMID: 15607294
12. Herpertz SC, Huebner T, Marx I, Vloet TD, Fink GR, et al. Emotional processing in male adolescents with childhood-onset conduct disorder. J Child Psychol Psychiatry. 2008; 49: 781–791. doi: 10.1111/j.1469-7610.2008.01905.x PMID: 18598245
13. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995; 34: 537–541. PMID: 8524021
14. Mantini D, Perrucci MG, Del Gratta C, Romani GL, Corbetta M. Electrophysiological signatures of resting state networks in the human brain. Proc Natl Acad Sci U S A. 2007; 104: 13170–13175. PMID: 17670949
15. Lu H, Zuo Y, Gu H, Waltz JA, Zhan W, et al. Synchronized delta oscillations correlate with the resting-state functional MRI signal. Proc Natl Acad Sci U S A. 2007; 104: 18265–18269. PMID: 17991778
16. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, et al. A default mode of brain function. Proc Natl Acad Sci U S A. 2001; 98: 676–682. PMID: 11209064
17. Zang YF, He Y, Zhu CZ, Cao QJ, Sui MQ, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain & development. 2007; 29: 83–91.
18. Tomasi D, Wang GJ, Volkow ND. Energetic cost of brain functional connectivity. Proc Natl Acad Sci U S A. 2013; 110: 13642–13647. doi: 10.1073/pnas.1303346110 PMID: 23898179
19. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. Nature. 2001; 412: 150–157. PMID: 11449264
20. Lui S, Yao L, Xiao Y, Keedy SK, Reilly JL, et al. Resting-state brain function in schizophrenia and psychotic bipolar probands and their first-degree relatives. Psychol Med. 2015; 45(1):97–108. doi: 10.1017/S003329171400110X PMID: 25066779
21. Kublbock M, Woletz M, Hoflich A, Sladky R, Kranz GS, et al. (2014) Stability of low-frequency fluctuation amplitudes in prolonged resting-state fMRI. Neuroimage. 2014; 103:249–57. doi: 10.1016/j.neuroimage.2014.09.038 PMID: 25251869

22. Fairchild G, Van Goozen SH, Calder AJ, Stollery SJ, Goodyer IM. Deficits in facial expression recognition in male adolescents with early-onset or adolescence-onset conduct disorder. J Child Psychol Psychiatry. 2009; 50: 627–636. doi: 10.1111/j.1469-7610.2008.02020.x PMID: 19432683

23. Bowen KL, Morgan JE, Moore SC, van Goozen SH. Young Offenders' Emotion Recognition Dysfunction Across Emotion Intensities: Explaining Variation Using Psychopathic Traits, Conduct Disorder and Offense Severity. J Psychopathol Behav Assess. 2014; 36:60–73. PMID: 24610972

24. Dadds MR, Perry Y, Hawes DJ, Merz S, Riddell AC, et al. Attention to the eyes and fear-recognition deficits in child psychopathy. Br J Psychiatry. 2006; 189: 280–281. PMID: 16946366

25. Schutter DJ, van Bokhoven I, Vanderschuren LJ, Lochman JE, Matthys W. Risky decision making in substance dependent adolescents with a disruptive behavior disorder. J Abnorm Child Psychol. 2011; 39: 333–339. doi: 10.1007/s10802-010-9475-1 PMID: 21153697

26. Sarinopoulos I, Grupe DW, Mackiewicz KL, Herrington JD, Lor M, et al. Uncertainty during anticipation modulates neural responses to aversion in human insula and amygdala. Cereb Cortex. 2010; 20: 929–940. doi: 10.1093/cercor/bhp155 PMID: 19679543

27. Platt ML, Huettel SA. Risky business: the neuroeconomics of decision making under uncertainty. Nat Neurosci. 2008; 11: 398–403. doi: 10.1038/nn2062 PMID: 18368046

28. Preuschoff K, Quartz SR, Bossaerts P. Human insula activation reflects risk prediction errors as well as risk. The Journal of neuroscience. 2008; 28: 2745–2752. doi: 10.1523/JNEUROSCI.4286-07.2008 PMID: 18337404

29. Volz KG, Schubotz RI, von Cramon DY. Predicting events of varying probability: uncertainty investigated by fMRI. Neuroimage. 2003; 19: 271–280. PMID: 12814578

30. Hsu M, Bhatt M, Adolphs R, Tranel D, Camerer CF. Neural systems responding to degrees of uncertainty in human decision-making. Science. 2005; 310: 1680–1683. PMID: 16339445

31. Hyatt CJ, Haney-Caron E, Stevens MC. Cortical thickness and folding deficits in conduct-disordered adolescents. Biol Psychiatry. 2012; 72: 207–214. doi: 10.1016/j.biopsych.2011.11.017 PMID: 22209639

32. Passamonti L, Fairchild G, Fornito A, Goodyer IM, Nimmo-Smith I, et al. Abnormal anatomical connectivity between the amygdala and orbitofrontal cortex in conduct disorder. PloS one. 2012; 7: e48789. doi: 10.1371/journal.pone.0048789 PMID: 23144970

33. Passamonti L, Fairchild G, Goodyer IM, Hurford G, Hagan CC, et al. Neural abnormalities in early-onset and adolescence-onset conduct disorder. Arch Gen Psychiatry. 2010; 67: 729–738. doi: 10.1001/archgenpsychiatry.2010.75 PMID: 20603454

34. Sasayama D, Hayashida A, Yamasue H, Harada Y, Kaneko T, et al. Neuroanatomical correlates of attention-deficit-hyperactivity disorder accounting for comorbid oppositional defiant disorder and conduct disorder. Psychiatry Clin Neurosci. 2010; 64: 394–402. doi: 10.1111/j.1440-1819.2010.02102.x PMID: 20546170

35. Tiet QQ, Wasserman GA, Loeber R, McReynolds LS, Miller LS. Developmental and sex differences in types of conduct problems. Journal of Child and Family Studies. 2001; 10: 181–197.

36. Schneider S, Peters J, Bromberg U, Brassen S, Menz MM, et al. Boys do it the right way: sex-dependent amygdala lateralization during face processing in adolescents. Neuroimage. 2011; 56: 1847–1853. doi: 10.1016/j.neuroimage.2011.02.019 PMID: 21316467

37. Moffitt TE. Sex differences in antisocial behaviour: Conduct disorder, delinquency, and violence in the Dunedin Longitudinal Study: Cambridge University Press. 2001

38. Silverthorn P, Frick PJ. Developmental pathways to antisocial behavior: The delayed-onset pathway in girls. Development and psychopathology. 1999; 11: 101–126. PMID: 10208358

39. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997: 36: 980–988. PMID: 9204677

40. Shanee N, Apter A, Weizman A. Psychometric properties of the K-SADS-PL in an Israeli adolescent clinical population. Isr J Psychiatry Relat Sci. 1997; 34: 179–186. PMID: 9334522

41. Zhou J, Chen C, Wang X, Cai W, Zhang S, et al. Psychiatric disorders in adolescent boys in detention: a preliminary prevalence and case–control study in two Chinese provinces. Journal of Forensic Psychiatry & Psychology. 2012; 23: 664–675.

42. Su L, Wang K, Fan F, Su Y, Gao X. Reliability and validity of the screen for child anxiety related emotional disorders (SCARED) in Chinese children. J Anxiety Disord. 2008; 22: 612–621. PMID: 17628391

43. Birleson P, Hudson I, Buchanan DG, Wolff S. Clinical evaluation of a self-rating scale for depressive disorder in childhood (Depression Self-Rating Scale). J Child Psychol Psychiatry. 1987; 28: 43–60. PMID: 3558538

44. Zhou J, Witt K, Zhang Y, Chen C, Qiu C, et al. Anxiety, depression, impulsivity and substance misuse in violent and non-violent adolescent boys in detention in China. Psychiatry Res. 2014; 216: 379–384. doi: 10.1016/j.psychres.2014.01.024 PMID: 24612970

45. Zhou J, Witt K, Chen C, Zhang S, Zhang Y, et al. High impulsivity as a risk factor for the development of internalizing disorders in detained juvenile offenders. Compr Psychiatry. 2014; 55: 1157–1164. doi: 10.1016/j.comppsych.2014.03.022 PMID: 24799260

46. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proceedings of the National Academy of Sciences of the United States of America. 1992; 89: 5675–5679. PMID: 1608978

47. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proceedings of the National Academy of Sciences of the United States of America. 1992; 89: 5951–5955. PMID: 1631079

48. Weissenbacher A, Kasess C, Gerstl F, Lanzenberger R, Moser E, et al. Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. Neuroimage. 2009; 47: 1408–1416. doi: 10.1016/j.neuroimage.2009.05.005 PMID: 19442749

49. Han Y, Wang J, Zhao Z, Min B, Lu J, et al. Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnestic mild cognitive impairment: a resting-state fMRI study. Neuroimage. 2011; 55: 287–295. doi: 10.1016/j.neuroimage.2010.11.059 PMID: 21118724

50. Lowe MJ, Mock BJ, Sorenson JA. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. Neuroimage. 1998; 7: 119–132. PMID: 9558644

51. Nie NH, Bent DH, Hull CH. SPSS: Statistical package for the social sciences: McGraw-Hill New York. 1975.

52. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Human brain mapping. 2002; 15: 1–25. PMID: 11747097

53. Ledberg A, Akerman S, Roland PE. Estimation of the probabilities of 3D clusters in functional brain images. Neuroimage. 1998; 8: 113–128. PMID: 9740755

54. Yao N, Cheung C, Pang S, Shek-Kwan Chang R, Lau KK, et al. Multimodal MRI of the hippocampus in Parkinson's disease with visual hallucinations. Brain Struct Funct. 2014. doi: 10.1007/s00429-014-0907-5

55. Sebastian CL, McCrory EJ, Cecil CA, Lockwood PL, De Brito SA, et al. Neural responses to affective and cognitive theory of mind in children with conduct problems and varying levels of callous-unemotional traits. Arch Gen Psychiatry. 2012: 69: 814–822. doi: 10.1001/archgenpsychiatry.2011.2070 PMID: 22868935

56. Robinson JL, Laird AR, Glahn DC, Lovallo WR, Fox PT. Metaanalytic connectivity modeling: delineating the functional connectivity of the human amygdala. Hum Brain Mapp. 2010: 31: 173–184. doi: 10.1002/hbm.20854 PMID: 19603407

57. Roy AK, Shehzad Z, Margulies DS, Kelly AM, Uddin LQ, et al. Functional connectivity of the human amygdala using resting state fMRI. Neuroimage. 2009: 45: 614–626. doi: 10.1016/j.neuroimage.2008.11.030 PMID: 19110061

58. Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR. Neocortical modulation of the amygdala response to fearful stimuli. Biol Psychiatry. 2003: 53: 494–501. PMID: 12644354

59. Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. Neuroimage. 2004: 23: 483–499. PMID: 15488398

60. Craig AD. How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci. 2009: 10: 59–70. doi: 10.1038/nrn2555 PMID: 19096369

61. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007: 164: 1476–1488. PMID: 17898336

62. Osuch EA, Willis MW, Bluhm R, Group CNS, Ursano RJ, et al. Neurophysiological responses to traumatic reminders in the acute aftermath of serious motor vehicle collisions using [15O]-H2O positron emission tomography. Biol Psychiatry. 2008: 64: 327–335. doi: 10.1016/j.biopsych.2008.03.010 PMID: 18423575

63. Mickley Steinmetz KR, Addis DR, Kensinger EA. The effect of arousal on the emotional memory network depends on valence. Neuroimage. 2010: 53: 318–324. doi: 10.1016/j.neuroimage.2010.06.015 PMID: 20542121

64. Zou QH, Zhu CZ, Yang Y, Zuo XN, Long XY, et al. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. J Neurosci Methods. 2008: 172: 137–141. doi: 10.1016/j.jneumeth.2008.04.012 PMID: 18501969

65. Stillova K, Jurak P, Chladek J, Halamek J, Telecka S, et al. The posterior medial cortex is involved in visual but not in verbal memory encoding processing: an intracerebral recording study. J Neural Transm. 2013; 120: 391–397. doi: 10.1007/s00702-012-0890-z PMID: 22968598

66. Takeuchi H, Taki Y, Nouchi R, Sekiguchi A, Hashizume H, et al. Resting state functional connectivity associated with trait emotional intelligence. Neuroimage. 2013; 83: 318–328. doi: 10.1016/j.neuroimage.2013.06.044 PMID: 23792978

67. Roland PE, Gulyas B. Visual memory, visual imagery, and visual recognition of large field patterns by the human brain: functional anatomy by positron emission tomography. Cereb Cortex. 1995; 5: 79–93. PMID: 7719132

68. Scherpiet S, Bruhl AB, Opialla S, Roth L, Jancke L, et al. Altered emotion processing circuits during the anticipation of emotional stimuli in women with borderline personality disorder. Eur Arch Psychiatry Clin Neurosci. 2014; 264: 45–60. doi: 10.1007/s00406-013-0444-x PMID: 24100929

69. Dalwani MS, Tregellas JR, Andrews-Hanna JR, Mikulich-Gilbertson SK, Raymond KM, et al. Default mode network activity in male adolescents with conduct and substance use disorder. Drug Alcohol Depend. 2014; 134: 242–250. doi: 10.1016/j.drugalcdep.2013.10.009 PMID: 24210423

70. Said CP, Haxby JV, Todorov A. Brain systems for assessing the affective value of faces. Philos Trans R Soc Lond B Biol Sci. 2011; 366: 1660–1670. doi: 10.1098/rstb.2010.0351 PMID: 21536552

71. Deeley Q, Daly E, Surguladze S, Tunstall N, Mezey G, et al. Facial emotion processing in criminal psychopathy. Preliminary functional magnetic resonance imaging study. Br J Psychiatry. 2006; 189: 533–539. PMID: 17139038

72. Fairchild G, Hagan CC, Passamonti L, Walsh ND, Goodyer IM, et al. Atypical neural responses during face processing in female adolescents with conduct disorder. J Am Acad Child Adolesc Psychiatry. 2014; 53: 677–687 e675. doi: 10.1016/j.jaac.2014.02.009 PMID: 24839886

73. Qiao Y, Xie B, Du X. Abnormal response to emotional stimulus in male adolescents with violent behavior in China. Eur Child Adolesc Psychiatry. 2012; 21: 193–198. doi: 10.1007/s00787-012-0252-2 PMID: 22297661

74. Golay X, Guenther M. Arterial spin labelling: final steps to make it a clinical reality. MAGMA. 2012; 25: 79–82. doi: 10.1007/s10334-012-0308-9 PMID: 22382350

75. Banich MT, Crowley TJ, Thompson LL, Jacobson BL, Liu X, et al. Brain activation during the Stroop task in adolescents with severe substance and conduct problems: A pilot study. Drug Alcohol Depend. 2007; 90: 175–182. PMID: 17499456

76. Schiffer B, Pawliczek C, Mu Ller B, Forsting M, Gizewski E, et al. Neural mechanisms underlying cognitive control of men with lifelong antisocial behavior. Psychiatry Res. 2014; 222: 43–51. doi: 10.1016/j.pscychresns.2014.01.008 PMID: 24530294

77. Moffitt TE (1990) Juvenile delinquency and attention deficit disorder: boys' developmental trajectories from age 3 to age 15. Child Dev 61: 893–910. PMID: 2364762

78. Wallace GL, White SF, Robustelli B, Sinclair S, Hwang S, et al. Cortical and subcortical abnormalities in youths with conduct disorder and elevated callous-unemotional traits. J Am Acad Child Adolesc Psychiatry. 2014; 53: 456–465 e451. doi: 10.1016/j.jaac.2013.12.008 PMID: 24655655

79. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007; 8: 700–711. PMID: 17704812