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1	Left Hippocampus to Anterior Cingulate Cortex Connectivity Correlates with
2	Worse Recent Verbal Memory in Pornography Addicted Juveniles
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31	Competing interest

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58 ABSTRACT

59	Background and aims: Imperil by the convenience of information and knowledge
60	access, children exposed to pornography have worsened. As such, this study aims to
61	gain insight into brain connectivity and cognitive function effect of pornography
62	addiction in juveniles, as the best of our knowledge, this study is the first to
63	specifically learn about memory function in juvenile's pornography addiction.
64	Methods: We screened 30 juveniles with 4 dropouts (13 non-addiction vs 13
65	addiction group). Subjects underwent neuropsychiatric tests (memory, attention, and
66	intelligence) and fMRI image acquisition. We carried correlation analysis of brain
67	connectivity and neuropsychiatric test results.
68	Results: Significant disconnection between left hippocampus to ACC (Z-
69	transformed r-value, non-addiction vs addiction = 0.07 ± 0.19 vs -0.08 ± 0.17 ,
70	p=0.04, cohen d=0.83) followed by worse verbal recent memory in pornography
71	addicted juveniles (RAVLT A6 sub-score, p <0.01, d=0.67; A7 sub-score, p=0.01).
72	Attention and intelligence test resulted to insignificant correlation.
73	Discussion: This data-driven analysis result strongly promotes the involvement of
74	cortico-subcortical systems in pornography addiction, emphasizing the role of reward
75	system pathology, indifferent to addiction pathophysiology in general. Decline in
76	working memory, which are maintained by corticolimbic network, including
77	hippocampus and ACC, affects goal-oriented behaviour greatly. This, correspond to
78	our significant result of addiction group's decline in memory, regardless of its
79	association with attention and intelligence.
80	Conclusion: Disconnection between left hippocampus to ACC suggested similar
81	neurobiological abnormalities as seen on other addictive disorders. Its disconnection

- 82 was also correlated with worse verbal recent memory in pornography addicted
- ⁸³ juveniles, without affecting attention and intelligence, results showed.
- 84 Keywords: Addiction, Juvenile, Pornography, Brain Connectivity, Cognitive
- 85 Function
- 86

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ABBREVIATION LISTS 88

89	ACC = Anterior Cingulate Cortex; ASAM = American Society of Addiction
90	Medicine; dACC = Dorsal Anterior Cingulate Cortex; DMN = Default Mode
91	Network; fMRI = Functional Magnetic Resonance Imaging; FOV = Field of View;
92	ICA = Independent Component Analysis; MCC = Midcingulate Cortex; MNI =
93	Montreal Neurological Institute; NFC = Negative Functional Connectivity; PCC =
94	Posterior Cingulate Cortex; PFC = Prefrontal Cortex; RAVLT = Ray Auditory Verbal
95	Learning Test; ROCFT = Ray-Osterrieth Complex Figure Test; ROI = Region of
96	Interest; TE = Echo Time; TMT = Trail Making Test; TR = Repetition Time; WISC
97	IQ = Wechsler Intelligence Scale for Children for IQ; YKBH = Yayasan Kita Dan
98	Buah Hati

99

INTRODUCTION 100

Era of globalization, which eases access to information and knowledge through the 101 102 Internet, has unfortunately exposed our children to pornography, intentionally or unintentionally. Unintentional exposure may risks from mistyping website addresses, 103 searching for terms with or without sexual meaning, or accidentally encountering 104 pop-up images and advertisements [1]. In virtue of this matter, it is important to 105 consider developmental factors in cognitive processing, as children aged less than 7 106 107 years old, have difficulty in differentiating between the on-screen and real-life situation. Incomplete cognitive development of children and adolescents may pose 108 real risks in affecting how pornography itself is perceived and acted upon by children 109 110 in their daily life, thus in turn may develop into problematic behaviours [2]. Problematic sexual behaviour in young children aged under 12 years old are thought 111

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to be the results of several factors, of which is pornography viewing, a study showed[3].

Studies in U.S. showed pornography exposure in children varies between studies, 114 with unintentional exposure ranged from 19-34% [4 - 6], and intentional exposure 115 43% [4]. Indonesia is no exception, in 2012, at least 50% Indonesian juveniles aged 116 10-19 v.o. has viewed pornography contents, 14% intentionally exposed. This 117 became worse in 2016, where at least 97% elementary students of 4-6th grade in 118 Jakarta and its surrounding had been exposed to pornography [7]. 119 120 Since long ago, substance addiction has gathered significant interests of both researchers and social activists. However, there are still very few studies concerning 121 pornography addiction, especially in the field of neuroscience. Addiction are thought 122 123 to be affiliated with the reward system of the brain, which involves emotion and executive functions of the brain--the amygdala, hippocampus, and frontal cortex [8, 124 9]. Studies have found that dysfunction in prefrontal cortex (PFC), a region of brain, 125 is accounted for the reduction in executive functions and behavioural inhibitory 126 control [10 - 12]. Despite the lack of neuroscientific studies of pornography 127 addiction, even more studies focusing on the younger population, a growing body of 128 evidence suggests that the mechanism behind pornography addiction is indifferent of 129 substance addiction, i.e. both involves disruption in PFC area [13 - 15]. The 130 131 involvement of both emotion and executive functions in neurobiology of addiction are thought to be connected through the broader form of corticolimbic network, in 132 which are anterior cingulate cortex (ACC), hippocampus, and prefrontal cortex 133 (PFC) that may intercorrelate with each other [8, 16, 17]. 134 As those affected areas turns into decline, it may affect its function, in this matter are 135 the children's and adolescents' who have still substantial room of growth in life, 136

137	therefore may lead them to life with cognitive or behavioural problems. Studies also
138	found that pornography addiction is among the causes of social problems [18,19].
139	The lack of scientific studies addressing these arising problem of the youths concerns
140	us. Therefore, this study aimed to use functional MRI in investigating brain
141	connectivity, especially in the area of PFC, ACC, and hippocampus, which thought
142	to be much affected; and its possible disruption of affiliated cognitive function-
143	memory, intelligence, and attentionin pornography addicted juveniles.
144	
145	MATERIALS AND METHODS
146	Participants
147	We used the data from 30 juveniles aged 12-16 years old from our previous study,
148	recruited during December 2017-February 2018, in various events held by YKBH in
149	Bekasi, Indonesia. Subjects were grouped into pornography addiction and non-
150	addiction group, which were determined using Pornography Addiction Test, a
151	battery of neuropsychological test designed and validated by YKBH [20]. Exclusion
152	criteria were left-handed, incomplete tests/fMRI procedures, verbal or language
153	disorder, history of brain-related disorder or disease, head trauma, trauma during
154	pregnancy or birth, developmental, psychological or neurological disorder, or mental
155	illness.
156	
157	Procedures
158	All participants underwent pornography addiction screening, memory function
159	assessment by Ray Auditory Verbal Learning Test (RAVLT) for auditory-verbal
160	memory and Ray-Osterrieth Complex Figure Test (ROCFT) for visual memory,
161	Wechsler Intelligence Scale for Children for IQ (WISC IQ), and fMRI image

162	acquisition. Each subject underwent MRI scanning using a 3-Tesla scanner (GE
163	Advance Workstation 4.5). We first performed an initial scan to center the field of
164	view on the subject's brain. We then performed a 3D T1-weighted turbo field echo
165	scan for anatomical reference (repetition time $[TR] = 8.3$ ms; echo time $[TE] = 3.2$
166	ms; FOV = 240 mm; matrix size = 256×256 ; slice thickness = 3.0 mm, space 1 mm).
167	Lastly, we performed a gradient echo-planar sequence for functional imaging (TR =
168	3000 ms; TE = 30 ms; flip angle = 90 degrees; FOV = 240 mm; 36 x 3 mm slices;
169	space 1mm) which lasted for 7 minutes. Subjects were asked to refrain from any
170	psychoactive substance use and sexual activity during the 24 hours preceding fMRI.
171	
172	Measures
173	Pornography Addiction Screening
174	We completed the pornography addiction screening with a self-reported
175	questionnaire, which developed by expert psychologist. Several indicators commonly
176	found in juveniles with high pornography consumptions were emphasized, based on
177	field studies and literature researches. Those are grouped into three dimensions: 1)
178	time spent on pornography in the last six months, consisted of number of times,
179	frequency, and duration spent; 2) motivation to use pornography, consisted of factors
180	encouraging access to pornography, which includes sexual curiosity, emotional
181	avoidance, sensation seeking, and sexual pleasure; and 3) problematic pornography
182	use, consisted of functional and distress problems, excessive use, control difficulties,
183	and using to escape negative emotions. The questionnaire consisted of 92 items and
184	has been tested on 740 grade six to ten students in Indonesia, which further details
185	corresponded in an unpublished report (Table S1 and S2). Three additional questions
186	were added to minimize faking good possibility, thus we excluded subjects who

187	answered these according to social desire. Pornography addiction was defined as
188	those with weighted score greater than or equal to 32. Psychometric analysis exhibited
189	valid (CFA $>$ 1.96) and reliable (Cronbach's Alpha $>$ 0.7) for all items in the
190	questionnaire.
191	Being specially developed and adapted to juveniles population, the questionnaire was
192	very suitable for this pornography addiction study. Furthermore, the additional
193	questions to exclude subjects who faked good and forced choice technique questions
194	in this questionnaire allowed for less bias. The limitation of this questionnaire may be
195	its number of questions, as it may induce fatigue and boredom on the subjects.
196	Although it being specially adapted to juveniles population made it very suitable for
197	this study, its use in other context outside of juvenile pornography addiction may
198	require wording adjustment to make a better understanding of the vocabularies used.
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199	
199 200	Memory Assessments
	Memory Assessments All subjects underwent memory function assessment by Ray Auditory Verbal
200	-
200 201	All subjects underwent memory function assessment by Ray Auditory Verbal
200 201 202	All subjects underwent memory function assessment by Ray Auditory Verbal Learning Test (RAVLT) for auditory-verbal memory and Ray-Osterrieth Complex
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long recall, A7). Finishing the RAVLT, which would take approximately 30-40

213	minutes to complete, all subjects were requested to reproduce the figure from memory
214	of previous ROCFT. Attention, as a factor influencing working memory, [21,22] was
215	evaluated using Trail Making Test (TMT) A and B. The subjects were instructed to
216	connect a set of 25 dots of numbers (TMT A) and mix of numbers and letters,
217	alternately (TMT B), after finishing each 8-dot-set-sample. The time taken of each set
218	was recorded.
219	
220	Intelligence Measurements
221	All subjects' intelligence were measured by Wechsler Intelligence Scale for Children
222	for IQ (WISC IQ) that was designed for children between 5 and 16 years of age. The
223	test consists of 10 basic tests and 2 supplementary tests. Basic tests comprise of verbal
224	tests (information, vocabulary, arithmetic, comprehension and similarities) and
225	performance tests (picture completion, picture arrangement, block design, object
226	assembly, and digit symbol). Supplementary tests comprise of (verbal tests, digit
227	span, performance test and maze).
228	
229	Analysis
230	Imaging Analysis
231	Data pre-processing followed a standard pipeline, consisting of realignment and
232	unwarping, slice-timing correction, normalization, outlier detection, and finally
233	spatially smoothing (full width at half maximum = 10 mm) which resulted in both
234	functional and structural images in MNI-space. All were conducted using CONN
235	toolbox version 17.f (https://www.nitrc.org/projects/conn) in SPM version 12
236	(http://www.fil.ion.ucl.ac.uk/spm/). De-noising which consisted of removing white

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237	matter and cerebrospinal fluid noise with 5 dimensions each, scrubbing, motion
238	regression, band-pass filtering (0.01–0.10 Hz), and linear detrending was later
239	performed. Nine nuisance covariates (time-series predictors for global signal, white
240	matter, cerebrospinal fluid, and the six movement parameters) were sequentially
241	regressed from the time-series.
242	Previous studies have shown patients with pornography addiction have impaired
243	control and impulsivity, much associated with subcortical structures connectivity,
244	such as hippocampus, putamen, and anterior cingulate cortex, thus were chosen as the
245	seed regions and targets in ROI-to-ROI analysis (Fig 1).[8, 13, 23-26] Correlation
246	map was produced by computing the Pearson linear correlation coefficients between
247	the time course of signal in each ROI and the average signal of the seed. The process
248	was calculated using CONN. To elucidate significant connection in each ROI-to-ROI
249	group, one-sample T-Test were used. The ROI analysis would include the targets in
250	cases where it was revealed significant connections between target and seed regions,
251	which were defined anatomically from the MNI template.
252	
253	Fig 1. ROI seed (left hippocampus, green) and target (ACC, red), from (a) superior
254	view, and (b) left medial view.
255	
256	To improve the normality of the distribution, we converted the correlation coefficients
257	to Fisher's Z-transformed r-values. We then performed correlation analysis between
258	the resulting Z-transformed r-values of significant ROI-to-ROI analysis (non-
259	addiction vs addiction group) with the significant neuropsychiatric test and each
260	domain sub-scores. For that purpose, we performed Spearman rank test.

261

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262 Statistical Analysis

263	We used Mann-Whitney tests for comparison between groups. Correlation analysis
264	was performed using Spearman rank test. Statistical significance was assumed on
265	p-value of <0.05. Cohen d's effect size was also calculated for each result, assuming
266	d-value of >0.2 as small, >0.5 as medium, and >0.8 as large effect size. All statistical
267	analysis was performed SPSS version 21.

268

269 Ethical Approval

270 The study was approved by Health Research Ethical Committee of Faculty of

271 Medicine Universitas Indonesia (Clearance No. 1155/UN2.F1/ETIK/2017) and

272 conducted in accordance to Helsinki Declaration. No subject was confronted with

273 pornographic material in this study. Informed consent was obtained from all

274 participants, represented by respective parents.

275

276 **Results**

277 Demographic Data

From the initial 30 subjects, 4 was dropped due to incomplete fMRI data, resulting in

final 26 subjects (13 non-addiction vs 13 addiction group). Demographic and

neuropsychiatric test results were shown in Table 1. Age was matched between both

groups (p = 0.34). Among memory test results, there was significant difference in

282 RAVLT A6 subscore (non-addiction vs addiction, $A6 = 14.08 \pm 1.12$ vs $11.15 \pm$

283 2.19, p < 0.01, d = 1.68) and A7 subscore (A7 = 14.23 ± 0.93 vs 11.69 ± 2.63 , p =

0.01, d = 1.28). There was no significant difference between groups in other scores

of RAVLT, ROCFT, TMT A, TMT B, and WISC IQ results.

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288		Non-Addiction	Addiction	
289		(n=13)	(n=13)	р
290	Age	13.31 ± 1.03	13.77 ± 1.30	0.34
291	Sex (F:M)	6:7	5:8	
292	RAVLT A6	14.08 ± 1.12	11.15 ± 2.19	0.00*
293	RAVLT A7	14.23 ± 0.93	11.69 ± 2.63	0.01*
294	ROCFT	24.12 ± 4.90	22.73 ± 6.57	0.76
295	TMT A	39.38 ± 11.21	44.92 ± 15.64	0.43
296	TMT B	86.31 ± 26.74	96.23 ± 56.16	0.70
297	WISC Verbal IQ	102.46 ± 10.88	98.38 ± 13.85	0.44
298	WISC Perform IQ	105.46 ± 10.50	102.77 ± 12.50	0.78
299	WISC Full IQ	104.46 ± 9.04	98.77 ± 13.88	0.20
300	WISC Original IQ	114.44 ± 12.58	106.79 ± 19.97	0.26
301	* statistically signifi	cant (p < 0.05)		

Table 1. Demographic and neuropsychiatric tests comparison.

302

303 Brain Connectivity

304 From ROI-to-ROI analysis in CONN with non-addiction>addiction contrast, we

305 found one significant connection difference, which was left hippocampus to ACC (Z-

transformed r-value, non-addiction vs addiction = 0.07 ± 0.19 vs -0.08 ± 0.17 , p =

0.04, d = 0.83) (Fig 2). Thence, it showed hypoconnectivity between hippocampus to

308 ACC in addiction group.

309

310 Fig 2. Boxplot comparison of Left Hippocampus-ACC Z transformed r-values

311 connectivity between Non-Addiction and Addiction groups.

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312

313 Correlation Analysis

- 314 We performed Spearman rank test between significant neuropsychiatric test
- 315 (RAVLT A6 and A7 score) and Z-transformed r-value of significant connectivity
- 316 (left hippocampus to ACC) in pornography addiction group, and found significant
- 317 correlation with A6 (r = 0.43, p = 0.04, d = 0.67) but not A7 (p = 0.10) (Fig 3).

318

- 319 Figure 3. Scatterplot of Left Hippocampus-ACC Z transformed r-values
- 320 connectivity with A6 score of RAVLT.
- 321

322 **Discussion**

323 Addiction is explained by American Society of Addiction Medicine (ASAM) as a

324 primary, chronic disease of brain, related to reward, motivation, and memory circuit.

325 Dysfunction of such circuit leads to characteristic biological, psychological, social

326 and spiritual manifestations—thus reflected in an individual pathologically seeking

reward and/or relief by substance use or other behaviours.[27]

In terms of addiction pathophysiology, emotion and cognitive function have long been

329 ascribed taking part within. Mesolimbic dopamine pathway is thought affected the

neurobiology of addiction. The pathway particularly connects with three other key

regions to form integrated circuits, commonly called as the reward system: the

amygdala (emotions, includes positive and negative, also emotional memory),

hippocampus (long term memories processing and retrieval), and the frontal cortex

- 334 (behaviour coordination). As aforementioned above, mesolimbic dopamine pathway
- takes a role in addiction and reward system. A study showed continued release of
- dopamine into the reward system in individual compulsively watching internet

337	pornography that it promotes neuroplastic changes reinforcing the experience.
338	Excessive behaviours influenced neuroanatomical and reward system changes [8, 9].
339	Taking part in the reward system, hippocampus is important for long-term memory,
340	contextual, spatial, and emotional processing; whilst the executive function aspect
341	was taken in by the frontal cortex [8, 16, 28–30]. PFC is particularly the key for
342	aspects of working memory, temporal processing, decision making, flexibility and
343	goal-oriented behaviour. As connectivity is a key determinant to functional
344	intercourse within the brain, hippocampus-PFC's role has been ascribed in the broader
345	form of corticolimbic network, in which anterior cingulate cortex (ACC),
346	hippocampus, and PFC may intercorrelate with each other.[8, 16, 17] The cingulate
347	cortex is divided into four functionally distinctive regions, which comprises of
348	Broadmann's areas 24, 25, 32, and 33. It consists of the ACC, midcingulate cortex
349	(MCC) or dorsal anterior cingulate cortex (dACC), posterior cingulate cortex (PCC),
350	and retrosplenial cortex. Being a part of corticolimbic network, the cingulate cortex
351	has role both in emotional and cognitive function. ACC and dACC in particular is
352	thought to carry out reward-based decision making. It has been shown that ACC
353	receives projections from structures that process rewards, i.e. striatum, mesolimbic
354	dopamine system, dorsolateral prefrontal cortex, orbitofrontal cortex, and the
355	supplementary and primary motor cortices [31, 32].
356	Various evidence supports the interaction of hippocampus-PFC in reward learning,
357	thus intercorrelate with addiction and impulsivity [17,33]. Particular region in
358	hippocampus has been implicated in context-dependent process, which is the ventral
359	subiculum of the hippocampus. Studies have shown its inactivation decreases
360	reinstatement, thus marking its important role in drug-seeking behaviour [33]. Similar
361	process has been shown in other kinds of addiction, i.e. game, internet, and

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362	pornography addiction [8, 12, 17, 26, 34–36]. Decline in working memory affects
363	goal-oriented behaviour greatly, as aforementioned maintained by PFC and
364	corticolimbic network [8, 16], thus suggested the problem existence in pornography
365	addiction [37].
366	As shown in both internet and drug addiction, studies showed a clear link between
367	addiction and aberrant connectivity in response of inhibition network, resulting in
368	behavioural disorder that fail to inhibit unwanted actions, thus associated with poor
369	impulse control. Studies have revealed lower grey matter density, abnormal white
370	matter fractional anisotropy, reduced orbitofrontal cortical thickness, impaired brain
371	activity, and nonetheless decreased functional connectivity.[8, 38] A study showed
372	rather increased functional connectivity in right hippocampus, and decreased
373	functional connectivity in right dACC and left caudate in the DMN. This abnormal
374	functional organization of the DMN are discussed as addiction-related increased
375	memory processing with decreased cognitive control-thus once again implying lack
376	of impulse control, self-monitoring, and attention [36].
377	Of various studies about addiction, many showed consistent findings in which
378	decreased functional connectivity in reward processing circuit, nonetheless between
379	hippocampus and ACC. Although drug addiction studies are appreciably more
380	dominating than other kinds of addiction, similar findings have also been shown on
381	other addictions, i.e. game, internet, and pornography addiction [8, 12, 17, 26, 34–36].
382	The first fMRI study focusing on internet pornography addiction was published in
383	2014 and showed the same brain activity as seen in substance addicts and alcoholics
384	[23].
385	Evidence of decreased brain functional connectivity is consistent with current models

386 emphasizing the role of reward system pathology in addiction. This data-driven

387	analysis result strongly promotes the involvement of cortico-subcortical systems in
388	pornography addiction as the fact it emerged as the prominent pathology. Thus,
389	indicating similar neurobiological characteristics with other addictive disorders, as
390	such subcortical regions may play the core role of brain network pathology.
391	Our study specifically enlisted juveniles as our focus of research, thus, being the first
392	to specifically learn about memory function in juvenile's pornography addiction, we
393	were unable to directly compare our results to previous studies. Thence, we attempted
394	to compare our results with other related studies. Our correlation analysis showed
395	significant results in RAVLT A6 and A7 sub-score. On the other hand, ROCFT,
396	which was to assess visual memory, showed no significant results. Attention,
397	considered as a factor influencing memory, also left with no significant results, as
398	seen on TMT A and B results. Attention ensures the selection of information we
399	received, and later selected to be brought into working memory from perception or
400	long term memory. That is to say, the two compounds do affect each other [39].
401	Therefore, our results exhibited significant decline in memory in addiction group,
402	regardless its association with attention considered. In addition, another cognitive test
403	that was assessed was WISC IQ test, also left no significant result. Therefore, it
404	showed that addiction affected visual-auditory memory of cognitive function without
405	affecting intelligence.
406	To hold up our results, previous studies had also found lower working memory in
407	substance addiction [40-42], but not pathological gambling [40, 41]. Study by Nie, et
408	al also showing similar decline in verbal memory of internet addiction group [43]. To
409	complement these results, we did correlation analysis and found significant
410	correlation of left hippocampus to ACC hypoconnectivity to RAVLT A6 sub-score
411	decline (r = 0.43, p = 0.04, d = 0.67). Similar results of unaffected intelligence in

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412	internet addiction and non-addition group were also found by Park, et al, also tested
413	with WISC IQ test with participants' mean age of 15.17 years old [44]. Considering
414	its pathology similarities with pornography addiction [8, 23], their similar results may
415	as well be regarded.
416	Our enrolment of juveniles participants serves both as our study's limitation and
417	strength. As our population size ($n = 13$ of each group) was rather small, to avoid
418	lacking in substantive significance, we also calculated the Cohen d's effect size of
419	each result. The effect size calculations show that the sample size of our study is
420	appropriate. Being the pioneer study of pornography addiction in juveniles, we aimed
421	to serve information for the most critical phase, in which are still growing and
422	developing juveniles' brains, thus might compensate underlying brain impairment.
423	
424	Conclusion
425	Our results suggest that adolescents with pornography addiction exhibit
426	disconnection between left hippocampus to ACC that greatly play a role in reward
427	system. This is consistent with other studies showing similar neurobiological
428	abnormalities between pornography addiction and other addictive disorders. Given to
429	its role in intelligence, memory, and learning, our results suggested that pornography
430	addiction in juveniles correlates with worse verbal recent memory. Although, we did
431	not find any significant correlation with intelligence and attention. Further research
432	with larger population might aid to more defined results.
433	
434	Supporting Information
435	Table S1. Mean performance on each of questionnaire's components and
436	concurrent validity, as opposed to the three-step-norm. The 92-item questionnaire

437 was followed by interview as qualitative input as well as questionnaire about children

438	tende	encies in sexual activities (Table S2) to confirm the screening (three-step-norm).		
439	Confirmatory factor analysis (CFA > 1.96) and Cronbach's Alpha (0.903; CA > 0.7)			
440	value	es showed its validity and reliability.		
441				
442	Table S2. Children tendencies in sexual activities questionnaire. It ranged from			
443		r to very frequent in a scale of 1 to 5. Minimum score of 11 and maximum score		
444 445	of 55			
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451	Conceptualization: PuP, REE, HE. Investigation: PuP, REE, HE, SEIS, NZA, DC.			
452	Methodology: PuP. Formal analysis: PeP, GFH. Resources: HE, SEIS, NZA, DC.			
453	Writing (draft preparation, review, and editing): PeP, GFH, PuP. All authors critically			
454	reviewed and approved the final version of the manuscript.			
455				
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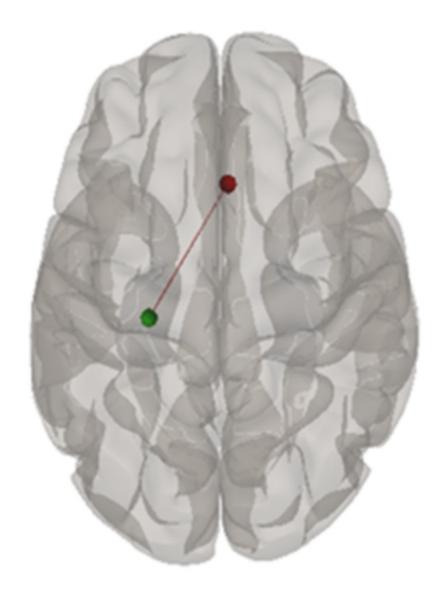
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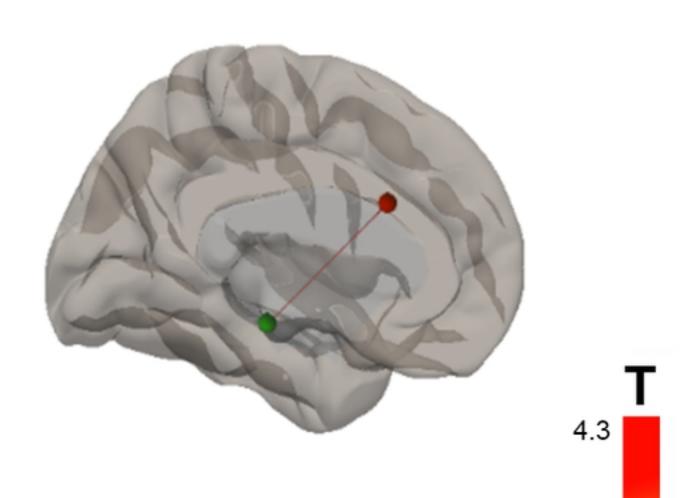
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Figure

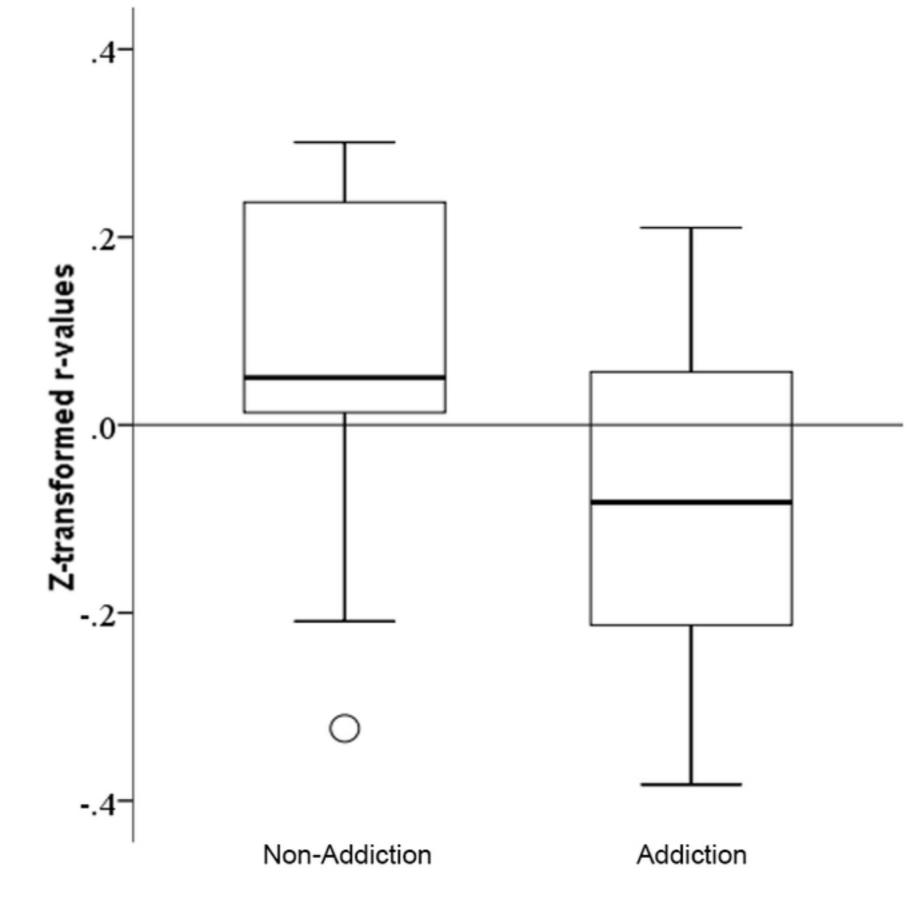


Figure 2

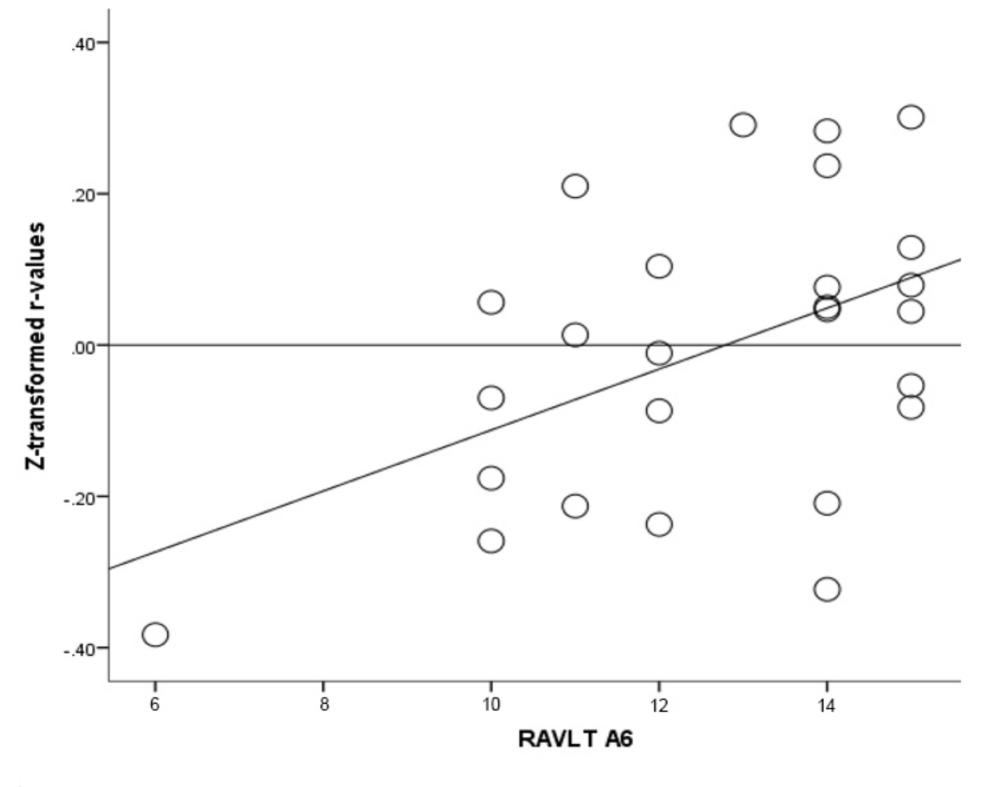


Figure 3