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Children's brain activation during risky decision-making: A contributor to substance problems?

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ABSTRACT

Objective: Among young children excessive externalizing behaviors often predict adolescent conduct and substance use disorders. Adolescents with those disorders show aberrant brain function when choosing between risky or cautious options. We therefore asked whether similarly aberrant brain function during risky decision-making accompanies excessive externalizing behaviors among children, hypothesizing an association between externalizing severity and regional intensity of brain activation during risky decision-making.

Method: Fifty-eight (58) 9–11 year-old children (both sexes), half community-recruited, half with substance-treated relatives, had parent-rated Child Behavior Checklist Externalizing scores. During fMRI, children repeatedly chose between doing a cautious behavior earning 1 point or a risky behavior that won 5 or lost 10 points. Conservative permutation-based whole-brain regression analyses sought brain regions where, during decision-making, activation significantly associated with externalizing score, with sex, and with their interaction.

Results: Before risky responses higher externalizing scores were significantly, negatively associated with neural activation (*t*'s: 2.91–4.76) in regions including medial prefrontal cortex (monitors environmental reward-punishment schedules), insula (monitors internal motivating states, *e.g.,* hunger, anxiety), dopaminergic striatal and midbrain structures (anticipate and mediate reward), and cerebellum (where injuries actually induce externalizing behaviors). Before cautious responses there were no significant externalizing:activation associations (except in post hoc exploratory analyses), no significant sex differences in activation, and no significant sex-by-externalizing interactions.

Conclusions: Among children displaying more externalizing behaviors extensive decision-critical brain regions were hypoactive before risky behaviors. Such neural hypoactivity may contribute to the excessive real-life risky decisions that often produce externalizing behaviors. Substance exposure, minimal here, was a very unlikely cause.

1. Introduction

1.1. Background

Persisting childhood externalizing behaviors, including *e.g.*, temper tantrums, restlessness, aggression, and destructive acts, comprise risk factors for adolescent substance use disorder (SUD), conduct disorder, and adult antisocial problems (Fergusson et al., 2005; Moffitt et al., 2011; Zucker, 2008). Such externalizing behaviors, common in very young children, usually decline in prevalence during development, but about 8 percent of children have severe externalizing behaviors at age two with little desistence by age 12 (Fanti and Henrich, 2010). Genes influence the severity of externalizing problems (Hicks et al., 2013; Kendler et al., 2015), and high externalizing scores equate with "behavioral disinhibition … a highly heritable general propensity to not constrain behavior in socially acceptable ways, to break social norms and rules, and to take dangerous risks, pursuing rewards excessively despite dangers of adverse consequences" (Kupfer et al., 2013; Kupfer

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and Regier, 2013 (*p* 536)). Thus, excessive risk-taking (*e.g.,* aggression, destructiveness) is part of an externalizing disposition in children.

SUD and conduct disorder diagnoses also involve excessive decisions to do risky behaviors − behaviors that may result unpredictably in rewards, but also in adverse consequences. Indeed, those disorders' diagnostic criteria include such risky behaviors as using substances in hazardous situations, or despite risks of exacerbating physical or psychological problems, as well as frequent fighting, weapons fights, or robberies (Kupfer et al., 2013 Kupfer and Regier, 2013). Thus, risky behaviors in part *define* those diagnoses.

Risky behaviors usually have cautious alternatives; *e.g.,* a child may choose between sneaking out at night, vs. studying for tomorrow's test. Such alternatives force risky-vs.-cautious decisions. Unfortunately, many decision-making brain structures are hypoactive as adolescents with substance and/or conduct problems process risky-vs.-cautious decisions (Crowley et al., 2015; Heitzeg et al., 2014; Jones et al., 2016; Shanmugan et al., 2016). Reported regions have included, *e.g.*, portions of frontal pole, dorsolateral and medial prefrontal cortices, striatum, insula, parietal cortex, brain stem, and cerebellum. Similarly, during risky decision-making substance-using young adults also show hypoactivity that “may make it difficult for them to refrain from risky decisions” (Gowin et al., 2013).

Among young children who later will develop substance and conduct problems certain other aberrant brain patterns occur during oddball P300 (Iacono and Malone, 2011), Go/No-Go (Heitzeg et al., 2014; Norman et al., 2011; Wetherill et al., 2013), or monetary incentive delay (Schneider et al., 2012) testing. If (like adolescents with substance and conduct problems) young children with externalizing problems dysfunctionally process risky decisions, that childhood aberrancy would antedate – and perhaps contribute to – the risk-taking later involved in adolescent substance and conduct problems. Dysfunctional processing of risky decisions might then underlie the substance and conduct problems of adolescents, as well as those childhood externalizing behaviors that presage such problems.

1.2. Hypotheses

To assess that possibility we examined in elementary-school children the association between severity of externalizing behavior and regional intensity of neural activation during risky-vs.-cautious decision-making, using the same decision-making game that we had employed earlier in adolescents with severe substance and conduct problems (Crowley et al., 2015). Seeking children with minimal or no substance exposure, we recruited 9–11 year-olds, since many children who will develop substance problems are using regularly by age 13 (Young et al., 1995).

Orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) have long been recognized as major players in decision-making. For example, Kringelbach and Rolls (2004) wrote that OFC damage impairs “stimulus-reinforcement association and reversal, and decision-making”. Similarly, Benegal et al. (2007) found reduced gray-matter volume in the ACC of children considered (because of externalizing problems) to be at risk for developing alcoholism. Thus, our *a priori* hypothesis predicted “significant associations of [brain] activation levels with severity of Delinquent Problems” as children made risky-or-cautious decisions, with effects in (but not limited to) orbitofrontal and anterior cingulate cortices. Our predictions were two-tailed because, when the project began, it was not yet clear that neural hypoactivity was common in persons with externalizing problems. Because the Child Behavior Checklist (CBCL) Delinquent Problems scale is part of the CBCL Externalizing scale (Achenbach, 1991), and because the latter also includes items more appropriate to young children, we used that scale. We know of no previous studies examining relationships between childhood externalizing behaviors and neural activation intensity during risky-or-cautious decision-making.

Growing evidence from adolescents also had shown sex differences in both severity of externalizing behaviors (Dodge et al., 2006) and brain activation during risky decision-making (Crowley et al., 2015). Therefore, we additionally hypothesized that in these young children, neural activation patterns would show significant sex differences during risky-or-cautious decision-making.

2. Methods

Please check **Supplementary file**, which, under numbered paragraph headings like those here, provides important additional details.

2.1. Assent, consent

Assent from children and consent from parents or guardians, obtained prior to participation, was written and informed. All procedures were approved by the Colorado Multiple Institutional Review Board.

2.2. Participants

Inclusion-exclusion criteria required that boys and girls: be 9–11 years old; report minimal or no substance use on six Monitoring the Future questions; provide urine and saliva free of alcohol and multiple drugs before scanning, with females' urine also pregnancy-negative; possess IQ ≥ 80 and English skills sufficient for assent/consent; and be without common MRI exclusions (*e.g.,* implanted metal).

2.3. Recruitment

Seeking a wide range of externalizing scores, we recruited children in two ways: (*a*) Some lived in zip code neighborhoods frequently contributing adolescent patients to our substance treatment programs and had no sibling ever treated for substance problems; 40 such families provided assent/consent and 29 completed assessments. (*b*) Others had a first-degree relative treated in our SUD programs; 53 provided assent/consent and 29 completed assessments. Altogether, 93 families assented/consented; 58 completed all procedures.

2.4. Medication use

Four participants used medications and 47 did not. Seven early admissions were not asked (a design error).

2.5. Assessments

2.5.1. Child behavior checklist 4/18 (CBCL)

A parent rated the child on the Externalizing Scale (Achenbach, 1991). Items included, *e.g.,* “Drinks alcohol without parents' approval” and “Steals at home”. We chose this dimensionally-scored assessment over the dichotomous yes-no diagnoses of the then-current DSM-IV (Frances et al., 2000).

2.5.2. Monitoring the future (MTF) questions (Johnston et al., 1986)

Six questions addressed the early substance experimentation sometimes occurring at this age. We planned to exclude children reporting more than minimal use; none did.

2.5.3. Eysenck impulsivity scale (Eysenck et al., 1984)

Children answered questions such as, “Do you generally do and say things without stopping to think?", and “Do you sometimes break rules quickly and without thinking?"

2.5.4. Wechsler intelligence scale for children (Wechsler, 1991)

We estimated full scale IQ from Vocabulary and Matrix Reasoning subtests.

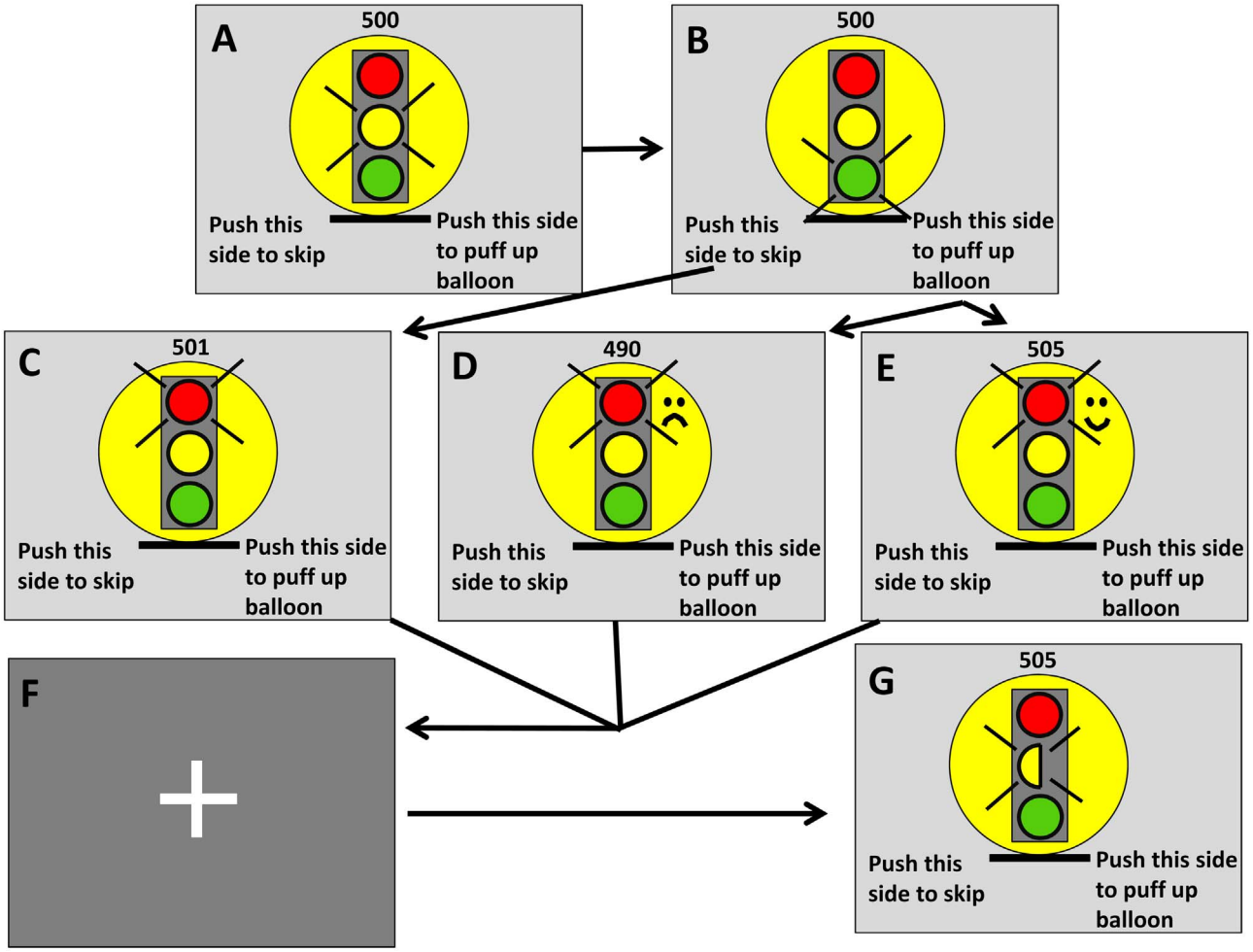

Fig. 1. Colorado Balloon Game, described in Methods. Modified from Crowley et al. (2015) with permission of the copyright-holding authors.

2.5.5. Lateral dominance (Reitan and Wolfson, 1985)

Lateral Dominance examinations identified left-handed participants.

2.6. Functional magnetic resonance imaging (fMRI) behavioral task

Children first viewed prizes to purchase with points earned in the game. In the magnet electronic goggles presented the Colorado Balloon Game (Crowley et al., 2010, 2015). Ninety Decision Trials each began with a 4 s deliberation period, signaled by a yellow light, for deciding between a risky right press or a cautious left press (Fig. 1A). Then, during a 0.5 s. green light (Fig. 1B), players executed their chosen press. During the following 3.5 s red light (with supporting sights and sounds), cautious presses added 1 point on the counter (Fig. 1C); risky presses either lost 10 points (Fig. 1D) or won 5 (Fig. 1E). The children were not informed that risky-press "win" probabilities decreased from 0.78 (game start) to 0.22 (end). Next, a "jittered" fixation screen (Fig. 1F) appeared for 2–4 s.

A paired Directed Trial followed each Decision Trial, although not necessarily immediately. A yellow half-light signaled its onset and directed which hand should respond to the green light (Fig. 1G; *e.g.,* left hand if left half lighted). Thereafter, each Directed Trial exactly replayed its paired Decision Trial (*i.e.*, Fig. 1B-F), except that the counter added two points for the correct directed response. Post-scan debriefings assessed game strategies and experiences.

2.7. MRI procedures

2.7.1. Image acquisition

In a 3T GE MRI scanner participants had a 3D T1 anatomical scan (IR-SPGR, TR = 9 ms, TE = 1.9 ms, TI = 500 ms, flip angle = 10°, matrix = 256 × 256, FOV = 220 mm^2, 124 1.7 mm thick coronal slices; 9 min 12 s), followed by 3 echo-planar (EPI) runs (TR = 2000 ms, TE = 26 ms, flip angle = 70°, FOV = 220 mm^2, 642 matrix, 36 slices, 4 mm thick, no gap, angled parallel to the planum sphenoidale, voxel size = 3.43 × 3.43 × 4 mm) separated by 1 min rests. Fast z-shimmed acquisition reduced inferior frontal susceptibility artifact (Du et al., 2007), capable of robustly showing orbitofrontal activation.

2.7.2. Preprocessing and single subject analyses

We conducted realignment, co-registration, spatial normalization, and smoothing (with 6 mm full-width half-maximum Gaussian kernel). For within-subject fMRI analyses we fitted preprocessed data with the general linear model (GLM) of Statistical Parametric Mapping (SPM) software, filtering low frequency noise, correcting for temporal autocorrelation using the autoregressive model (AR(1)), convolving with a single canonical HRF signal. A 128 s high pass filter removed signal drift and low-frequency fluctuation. The GLM model included separate trial periods, Decision (risky right or cautious left response) and Outcome (win or loss, not reported here). We generated single-subject contrast maps with SPM8, analyzing brain-function differences in contrasts of interest (*e.g.*, right-press Risky Decision Trial vs. right-press Sham-Risky Directed Trial) as fixed effects.

2.7.3. Motion criteria

During data collection and sample selection a highly experienced master's-level imaging engineer (co-author MSD) scrubbed from the data any spike of motion greater than 2 mm translational or 2 ° rotational; he dropped from the study participants subjectively judged to have excessive amounts of non-spike motion (see **Supplement**).

2.8. Main variables and analyses

During the 4 s deliberation period, Decision Trials differed from Directed Trials in requiring a decision; thus, *(Decision Trial – Directed Trial)*$_{Activation}$ assessed decision-related activation. Published Externalizing Scale T-scores (Achenbach, 1991) are sex-normed, so to facilitate sex comparisons we used raw scores (after natural logarithm (nlog) transformation).

We initially planned to combine the community recruits and the patient-relative recruits for a regression analysis, but before proceeding we examined whether the two groups had significantly different Externalizing scores. Since they did not, we proceeded with combined-group whole-brain regression analyses that assessed regional associations between the severity of children's externalizing scores vs. the intensity of their neural activation during risky-or-cautious decision-making. Our primary *pre hoc* analytic model was: Neural Activation = Ext + Sex + Ext*sex, where "Ext" = nlog(externalizing score + 1). We first sought regions with significant interactions. Finding none, we then evaluated the main effects of Ext and Sex. Our tables present only regions contributing 10 or more voxels to a cluster.

Similar to the procedures of Crowley et al. (2015), we removed from the sample any participant with fewer than 20 responses in any 30-trial run. No additional children were removed for excessive or deficient numbers of either risky or cautious responses, since those numbers could reflect important differences in brain function.

Motivated by Eklund et al. (2016), we applied nonparametric permutation testing using the SnPM toolbox (: www.go.warwick.ac.uk/tenichols/software/snpm (Accessed 11 November 2016); Nichols and Holmes, 2002) for the SPM software package. We conducted 10,000 permutations using a voxel level $p = 0.005$ and cluster-wise family-wise error (FWE) threshold of $p < 0.05$, applying variance smoothing (FWHM = 6 mm) to generate extent thresholds averaging 1215 voxels (voxel size = $2 \times 2 \times 2\,mm^3$) for the main effect of externalizing behavior vs. risky brain activation after adjusting for sex. The main assumption behind permutation testing is exchangeability, that under the null hypothesis relabeling of the data will have no effect. Thus, under those assumptions the regressor of interest is permuted while holding the other regressors fixed (Winkler et al., 2014), providing a distribution of statistical images. Multiple-comparisons were addressed with a null-distribution based on the maximum values from each of these images (Nichols and Hayasaka, 2003).

This study allowed participants to self-select which, and how many, of their choices would "go risky", or "go cautious". Therefore, following a reviewer's suggestion, we also performed secondary multiple regressions that explored the possible influence of more, or fewer, risky or cautious choices. In these exploratory analyses we additionally adjusted for participants' number of Risky responses (in the pre-Risky analysis), with the corresponding adjustment in the pre-Cautious analysis.

The **Supplementary file** provides additional analytic details.

3. Results

3.1. Sample summary

Fifty-eight children (27 males) described in Table 1 completed assessments. They reported zero-to-minimal substance exposure. Our MTF questions were chosen to reflect early, low-level substance experimentation, and we had planned to exclude any children with scores > 16. None approached that level. Fifty-two children scored 0; scores of 3, 2, or 1, were each generated by two children.

3.2. Relationships of neural activation with externalizing scores and sex

Before risky responses extensive brain regions showed significant negative associations between activation intensity and externalizing score (after adjusting for sex) (Table 2; Fig. 2; 3D Fig. 1 in **Supplement**). Those findings emerged *after* we showed that risky responses were preceded by neither significant externalizing-by-sex interactions, nor by sex differences in activation. Findings in the secondary analysis, which additionally adjusted for number of risky responses, closely paralleled those in the pre-hoc planned analysis (**Supplement** Section 3.2).

Before cautious responses our planned analyses yielded no significant findings in activation:externalizing associations, externalizing-by-sex interactions, nor in sex differences. However, the secondary analysis did suggest significantly-positive activation: externalizing associations in left posterior-medial structures (**Supplement** Section 3.2).

3.3. Data supporting these associations

Five observations supported these associations' validity

(a) Despite their young age, these children apparently understood the game. First, post-session debriefings revealed an understanding of the different trial expectations (Table 1, "Who told me which to press?" in Decision vs. Directed Trials, with 'myself' vs. "the computer" anchoring a Visual Analogue Scale). Second, the children reported (Table 1) considerable happiness in Decision Trials when balloons expanded (signaling "reward is coming"), less in Directed Trials when balloons expanded ("sham win, no reward coming"), and much less when Decision-Trial balloons popped ("loss is coming"). Third, without being told that the probability of losing after risky responses increased during the game, both sexes gradually learned to reduce risky responding (supporting data in **Supplement**).

(b) Fig. 3 shows that participants' range of externalizing scores exceeded 4 standard deviations, benefitting our regression analyses, which considered differences in activation:externalizing associations over the whole range of scores and used a logarithmic transformation to reduce the influence of very high scorers.

(c) Parent-rated externalizing scores and child-rated Eysenck Impulsiveness scores correlated moderately (Pearson $r = 0.42$; $p = 0.001$), tending to validate our use of the Externalizing Scale. Also, the Externalizing raw and T-scores (Fig. 3) correlated strongly ($r = 0.94$). Although not unexpected, this was reassuring because our regression analyses used raw scores.

(d) Strong sex differences would have complicated interpretation of the association findings. However, the sexes did not differ in the association of externalizing scores and activation intensity, nor in demographics, externalizing scores, nor most measures of game performance (Table 1).

(e) We separately explored potentially confounding correlations in each sex and in the combined sample. Externalizing scores did not correlate significantly with age, IQ, nor with numerous measures of game performance. Neither did age correlate with game performance.

4. Discussion

4.1. Main finding

As rated by parents, more-externalizing children in real life excessively chose risky (instead of cautious) behaviors. In our laboratory, as 9–11 year-old children were making decisions to do risky behaviors, those with higher externalizing scores generated significantly less

Table 1
Participant Characteristics and Game Performance.

	Male + Female	Male	Female	M:F Test[d]	*p*
n	58	27	31		–
Age (Years)[a]	10.6 (0.8)	10.6 (0.8)	10.6 (0.8)	t	*NS*
IQ estimate[a]	102.5 (11.5)	102.3 (11.0)	102.7 (12.2)	t	*NS*
Percent White	70.7	63.0	77.4	Chi-sq	*NS*
Number left-handed	4	1	3	FE	*NS*
Externalizing raw score[a]	6.9 (7.5)	7.9 (7.6)	5.9 (7.4)	MW	*NS*
Ext[a]	1.6 (1.0)	1.8 (1.0)	1.5 (1.0)	t	*NS*
Total score, 6 MTF substance-use questions[a]	0.21 (0.67)	0.15 (0.60)	0.26 (0.73)	MW	*NS*
Risky responses[a]	42.0 (13.4)	41.2 (13.3)	42.6 (13.8)	MW	*NS*
Risky responses, first 30-trial block[a]	17.3 (4.4)	16.7 (3.9)	17.8 (4.8)	t	*NS*
Cautious responses[a]	40.9 (15.0)	43.3 (14.1)	38.8 (15.6)	t	*NS*
Missed responses on Decision Trials[a]	7.1(6.2)	5.5 (6.4)	8.5 (5.8)	t	0.06
Missed responses on Directed Trials[a]	6.5 (6.1)	5.8 (6.1)	7.1 (6.2)	t	NS
Number of wins after Risky responses[a]	24.2 (7.1)	23.6 (6.8)	24.8 (7.4)	MW	*NS*
Total points earned[a]	651.4 (55.6)	653.4 (54.7)	649.7 (57.1)	t	*NS*
Green-light reaction times for risky responses[a]	292.0 (31.5)	289.9 (33.4)	293.9 (30.2)	t	*NS*
Green-light reaction times for cautious responses[a]	291.2 (33.3)	290.4 (30.2)	291.8 (36.3)	t	*NS*
Who told me which to press, Decision Trial[a,b]	5.4 (13.5)	6.9 (18.4)	4.1 (6.9)	t	*NS*
Who told me which to press, Directed Trial[a,b]	88.9 (22.8)	87.4 (23.3)	90.2 (22.5)	t	*NS*
Happy, when Balloon Puffs Up, DecisionTrial[a,c]	7.2 (10.3)	6.2 (10.1)	8.1 (10.6)	t	*NS*
Happy, when Balloon Pops, Decision Trial[a,c]	65.2 (17.2)	70.1 (15.8)	60.8 (17.4)	MW	***0.039***
Happy, when Balloon Puffs Up, Directed Trial[a,c]	21.8 (20.5)	19.0 (18.7)	24.4 (22.1)	t	*NS*
Happy, when Balloon Pops, Directed Trial[a,c]	40.9 (27.2)	42.0 (29.7)	40.0 (25.3)	t	*NS*

Abbreviations: Chi-sq, Chi Square. Ext, natural logarithm of (Externalizing raw score + 1). FE, Fisher Exact. MTF, Monitoring the Future survey. MW, Mann-Whitney test. NS, not significant. t, Student's *t*-test.

[a] Mean (SD).

[b] "I told myself" = 0 mm; "the computer told me" = 100 mm.

[c] "Really, really happy" = 0 mm; "Really, really sad" = 100 mm.

[d] Not corrected for multiple comparisons.

Table 2
Regions Where Neural Activation Intensity before Risky Responses Associated Significantly with Externalizing Score[a,b]. All Associations Are Negative.

Cluster Size[c]	Structure	BA or Side[d]	x[e]	y[e]	z[e]	t
3855	Inferior Frontal Gyrus	R,L 47	32	20	−6	4.76
	Insula	R,L 13	36	18	2	3.49
	Claustrum	R	30	16	4	3.18
	Caudate Head	R,L	−8	14	−2	3.70
	Anterior Cingulate	R,L 25	8	12	−10	3.08
	Putamen	R,L	14	12	−6	3.26
	Subcallosal Gyrus	R,L 34	8	6	−14	3.76
	Lateral Globus Pallidus	R	12	6	−2	3.24
	Caudate	R	8	6	8	2.91
	Midbrain (Subst N, VTA)	L	−6	−14	−12	3.87
	Midbrain (Incl. Red N)	R,L	−8	−12	−12	4.01
	Thalamus	R,L	20	−28	10	3.63
	Culmen	R,L	−10	−38	−18	2.95
2099	Anterior Cingulate	R,L 32	10	26	28	3.57
	Cingulate Gyrus	R,L 23,24,32	−2	−20	34	4.42
	Sup Fr Gyrus (Medial)	R,L 6,8,9,32	2	22	48	4.07

Abbreviations: BA, Brodmann Area. Incl., including. L, left. N, nucleus. R, right. Subst N, substantia nigra. Sup Fr, superior frontal. VTA, ventral tegmental area.

[a] Externalizing score (Ext) = Natural log(Externalizing Scale raw score + 1).

[b] Analytic model: $[(\text{Neural activation})_{\text{DecisionTrial}} - (\text{Neural activation})_{\text{DirectedTrial}}]$ = Ext + Sex + Ext*Sex. In full model we evaluated regions for significant interactions (found none). Then evaluated main adjusted effects of Ext and Sex.

[c] Voxels in cluster. Structures contributing < 10 voxels are not listed.

[d] If bilateral, the larger maximum is shown.

[e] Position of structure's maximally activated voxel: mm left or right (x), rostral or caudal (y), and superior or inferior (z) to anterior commissure.

neural activity in key decision-making structures. That externalizing-related neural hypoactivity *preceded* risky behaviors, a temporal relationship suggesting that the behavior did not cause the neural pattern, but that the aberrant neural pattern probably did contribute to the aberrant behavior, *i.e.,* the more-externalizing children's excessively risky real-life choices.

We note, however, that in this game greater externalizing was not associated with more risky responses. In a similar game antisocial adults did make more risky responses than comparison participants, but requiring 5 s of pre-response deliberation eliminated that difference (Newman et al., 1987). Our game's 4 s pre-response deliberation similarly may have reduced risky responses among the more-externalizing children, although the associated neural dysfunction apparently remained.

4.2. Are the findings inTable 2 valid?

Many of Table 2's listed regions play critical roles in decision-making, and less activation there clearly meant more externalizing, but can these results be trusted? Our first answer is that although many previous fMRI studies employed analyses prone to false-positive results, the permutation analyses used here are much more conservative (Eklund et al., 2016).

Moreover, our findings in young children are similar to those reported in recent *meta*-analyses of studies in older persons. Alegria et al. (2016) analyzed fMRI studies comparing youngsters (mean age 15 years) with or without disruptive behavior disorders. Participants with disorder had hypoactivation "in the rostro-dorsomedial, fronto-cingulate, and ventral striatal regions that mediate reward-based decision making", very closely overlapping our Table 2 regions.

Also, Raschle et al. (2015) reported two *meta*-analyses of studies examining adolescents with serious aggressive behavior. First, in volumetric studies aggression-associated deficiencies in gray-matter volume overlapped almost perfectly with regions in our Table 2. Second, most Table 2 structures also were present in a functional *meta*-analysis examining regional brain hypoactivity after emotionally-laden stimuli.

Another recent *meta*-analysis (Rogers and De Brito, 2016) examined studies comparing youths (9–21 years old) who either did, or did not, have conduct problems. Those with such problems had less gray-matter volume in several structures appearing in our Table 2: right anterior cingulate (Brodmann Area (BA) 32), left inferior frontal gyrus (BA 47), bilateral insula (BA 48/38 extending into BA 13), and bilateral superior

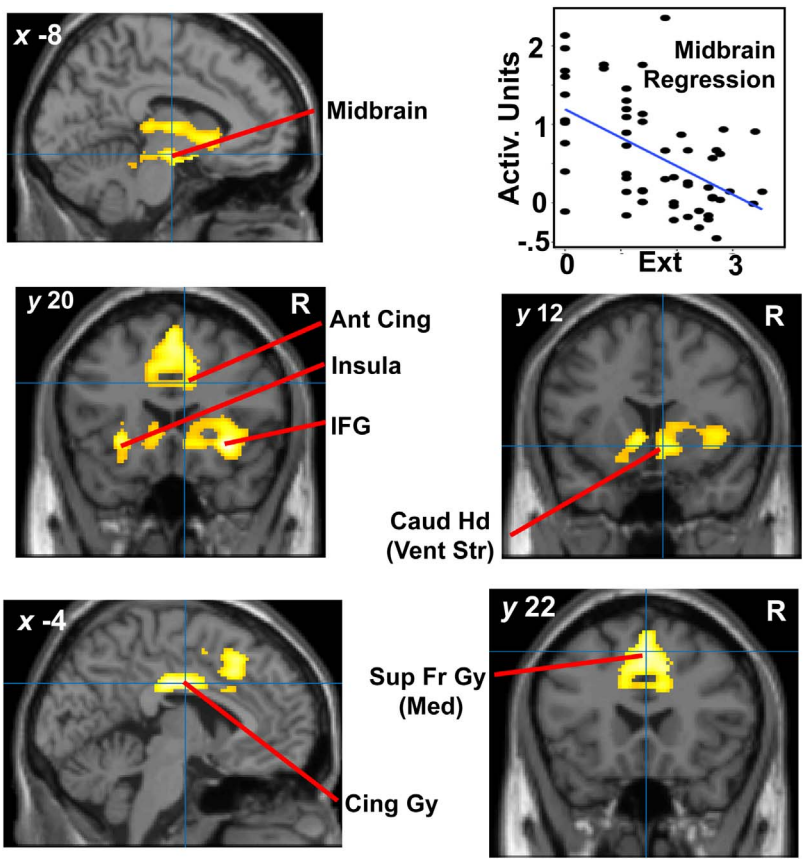

Fig. 2. Selected Brain Regions Displaying Significant Associations Between Externalizing Severity And Intensity Of Neural Activation Before Risky Responses. The regression for the midbrain site also appears. Abbreviations: *Activ. Units,* intensity of activation (see **Supplement** Section 2.8, Other Analytic Details). *Ant Cing*, anterior cingulate gyrus; *Caud Hd (Vent Str)*, caudate head (or ventral striatum); *Cing Gy*, cingulate gyrus; *Ext,* natural logarithm of (Externalizing raw score +1); *IFG*, inferior frontal gyrus; *R*, right; *Sup Fr Gy (Med)*, medial portion of the superior frontal gyrus; *x* and *y*, respectively, rostro-caudal and left-right positions in mm.

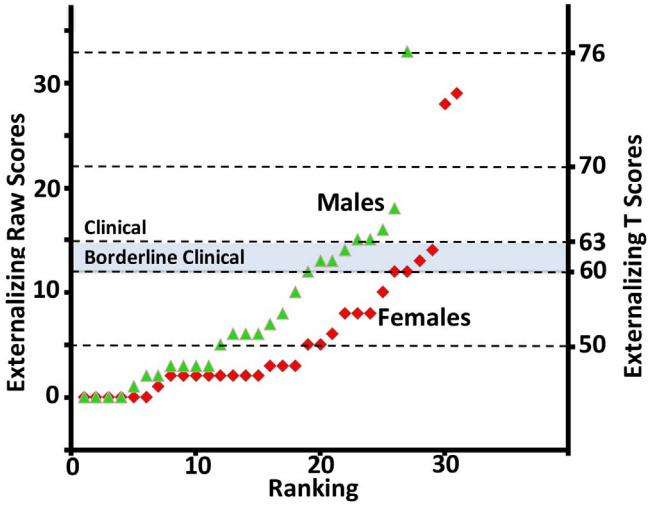

Fig. 3. Within-Gender Ranking By Child Behavior Checklist Externalizing Scores, 27 males, 31 females; four females overlap four males at zero. Left axis, raw scores. Right axis and dashed lines, boys' T scores. Despite some male-female scale differences, T-score 60 = raw score 12 for both sexes. Published norming group: 97.7 percent are below T-score 70; T scores 60–63, "Borderline Clinical"; > 63, "Clinical" (Achenbach, 1991).

frontal gyrus (medial, BA 10 extending into BA 9) (for the latter two: personal communication, Dr. Jack Rogers, 12 October 2016).

Therefore, brain regions showing structural deficiencies or functional hypoactivity in externalizing adolescents and young adults also showed functional hypoactivity in our much-younger externalizing children, strongly supporting our methods' validity. Looking in the other age direction, functional MRI studies like ours are difficult in even-younger children, but structural studies demand less from participants. Such a study (Fahim et al., 2011) of 8 year-old children with serious externalizing problems found cortical thinning in several brain regions (including anterior cingulate, cingulate, and insular cortices) where we found hypoactivation, providing further support for the validity of our findings.

It is known, of course, that childhood externalizing behaviors may persist into adolescent substance and conduct problems. However, considering our study with those above suggests that, also persisting into adolescence are *neural abnormalities of externalizing children, abnormalities antedating almost all substance exposures.*

4.3. Hypoactive regions interacting to impair goal-directed decision-making

How might the regions in Table 2 interact to regulate goal-directed decision-making in the Colorado Balloon Game? Buschman and Miller (2014) argue that "top-down control depends on a balance between quick but concrete, and gradual but abstract, learning". First, the evolutionarily old basal ganglia, densely innervated from the midbrain ventral tegmental area and substantia nigra, efficiently facilitate "quick, but concrete" stimulus-response learning, utilizing as "teaching signals" immediate reward-related increases, or loss-driven decreases, in dopamine release. In our participants the severity of externalizing scores was associated with the severity of hypoactivity in the reward-mediating midbrain (including the regions of substantia nigra and ventral tegmental area) and basal ganglia (including nucleus accumbens and other regions of caudate and putamen). Under-activity there supports arguments (*e.g.,* Sussman and Leventhal, 2014) that reward-system deficiencies may contribute later to excessive reward-seeking with drugs and risky behaviors.

The Buschman and Miller (2014) review further shows that the more evolved prefrontal areas receive less dense dopaminergic innervation, resulting in "slowly biasing connections, allowing learning to integrate over many [different] experiences and resulting in a more abstract representation". Accordingly, behavior control from prefrontal cortex includes not just stimulus-response associations, but also context

information useful for guiding future behavioral choices in unfamiliar situations. Eventually, when the behavior control that slowly develops in prefrontal cortex regularly results in reinforcement, that behavior becomes habitual and its control may shift to the basal ganglia. The medial prefrontal cortex (BA 6, 8, 9, 24, and 32) was hypoactive in our more-externalizing participants. That region monitors changing environmental reward-punishment schedules and signals when changes in behavior are needed to maximize reward (Ridderinkhof et al., 2004). It also is hypoactive in SUD patients during emotion regulation (Wilcox et al., 2016).

Insula also was hypoactive in our more-externalizing children. It monitors internal states such as hunger or anxiety, which modify the current value of possible rewards or punishments (Craig, 2009). Insula also predicts the probability of adverse outcomes from behavior choices (Preuschoff et al., 2008). Moreover, insula enjoys connections with almost every other site listed in Table 2 (Ghaziri et al., 2015), suggesting a role in coordinating those sites.

So different regions hypoactive in externalizing children have different functions, and we hypothesize that specific externalizing behaviors may arise from hypoactivity of those different regional functions: (a) More-externalizing children may have biologically impaired "quick, but concrete" stimulus-response learning in basal ganglia (*possible example:* repeated "stay-after-school" punishments do not improve classroom behavior). (b) The children's medial prefrontal cortices may inadequately store or retrieve context information for guiding behavior in new situations (*possible example:* learning to change behavior in response to one teacher's disapproving looks may not transfer to another teacher). (c) The medial prefrontal cortices of these children may insufficiently monitor changing reinforcement or punishment schedules for adaptive behavioral adjustments (*possible example:* the unrestrained talking allowed at home continues at school). (d) These children's insulae may maladaptively judge the value of rewards or punishments (*possible example:* a school suspension is actually welcomed). (e) Their insulae may not appropriately predict adverse outcomes from behaviors (*possible example:* candy is shoplifted despite a watching store owner).

4.4. Sex influences

Since risky behaviors are more common among young boys than girls (Fanti and Henrich, 2010), we hypothesized that these children would show regional sex differences of activation intensity during risky-or-cautious decision-making. However, sex differences in activation intensity, and in the association between activation intensity and externalizing severity, are not apparent in our data. They might, of course, appear in future studies with larger samples, where assessing pubertal stage also may add additional sensitivity.

4.5. Limitations

This study benefitted from using the Colorado Balloon Game, which (*a*) identified qualitatively different (*i.e.*, non-identical) activation patterns preceding risky and cautious behaviors, (*b*) reduced variability among participants by norming decision-related activation to a within-subject control condition (Directed Trials), and which (*c*) was understood by these young children. However, certain limitations also must be recognized.

First, adding teachers' ratings might have enhanced the externalizing scores' validity. Second, our discussion compares children reported here and adolescents reported elsewhere (Alegria et al., 2016; Raschle et al., 2015; Rogers and De Brito, 2016). Such cross-sectional comparisons should inform, but cannot replace, future longitudinal studies. Third, among such young children refusals, drop-outs, and exclusions for motion-flawed data were not uncommon, potentially biasing results, although validity is suggested by certain strong consistencies (*e.g.,* before risky behaviors *all* (of many) significant activation:externalizing associations were negative). And again, the similar neural dysfunction of these children and troubled adolescents (Alegria et al., 2016; Raschle et al., 2015; Rogers and De Brito, 2016), although unfortunate, is reassuring.

Fourth, we excluded neither left-handers nor medication users. Excluding medication users may specifically eliminate those higher-externalizing children of interest here, and even briefly withholding children's medications for non-treatment research may raise ethical concerns. Moreover, a recent large adolescent study found that excluding medicated youths had little effect on brain activation patterns (Shanmugan et al., 2016). Additionally, a large *meta*-analysis of adolescents with disruptive behavior disorders found no effect of medications on neural dysfunction (Alegria et al., 2016). Also, handedness does not alter externalizing-related frontal EEG asymmetry (*e.g.,* Gatzke-Kopp et al., 2014). However, more research is needed on these questions.

Fifth, we know that half of the studied children had at least one first degree relative with SUD, but we do not have full family-history density data on any subjects. While that does not detract from our report that brain activity and externalizing scores are associated, such data could provide a fuller description of participants in future studies.

Sixth, we used permutation analyses, since Eklund et al. (2016) showed that other widely-used procedures may inflate *p*-values. Indeed, earlier analyses of our data (not shown here), using procedures like those in our previous publications (*e.g.*, Crowley et al., 2015), indicated (as would be expected from less conservative methods) "significance" in all regions shown here, plus many more. However, eliminating possibly false-positive findings came at some cost. These permutation procedures would not recognize as significant any cluster (even a very strong "hot spot") of less than about 1215 voxels, so false-negative findings are possible.

Further questions about false-negative results arose when a reviewer suggested two secondary analyses. One added participants' number of risky responses as an additional covariate in the pre-Risky multiple regression, and the other added participants' number of cautious responses as an additional covariate in the pre-Cautious regression (**Supplement** Section 3.2).

The first of those analyses had little effect on the regions showing significantly negative activation:externalizing associations before risky responses. However, (**Supplement** Section 3.2) while our primary analysis had found no regions with significant associations before cautious responses, this exploratory analysis identified significantly positive left medial parietal and occipital associations. That region also was called "significant" in the less-conservative analyses mentioned in the previous paragraph. To address false-positive concerns, future studies might explore analytic procedures under development, such as "threshhold free cluster enhancement" (Smith and Nichols, 2009; Radua et al., 2014; Regner et al., 2015).

Seventh, space limitations prevent us from examining here the association of brain activity with broader task behaviors, such as number of risky responses. Future studies should address these questions.

Eighth, we (like Kahn et al., 2014) analyzed neural activations preceding risky responses separately from those preceding cautious responses, comparing each with an almost-identical, no-decision, baseline control condition (see **Supplement** Sections 2.8 and 4.5). That approach is not intended to, and cannot, prove statistically significant regional differences between risky and cautious choices. However, we note that only before risky choices did the approach identify extensive regions with negative externalizing:activation associations (Table 2).

5. Conclusions

Literature reviewed here, together with our data, highlight seven important suggestions about young children. (*a*) Excessively deciding to take risks is part of the externalizing disposition that places children in danger of future substance and conduct problems. (*b*) Genetics contribute strongly to children's externalizing dispositions. (*c*) That genetic

influence on behavior presumably is expressed through the brain. (*d*) Children's severity of externalizing problems varies negatively with the intensity of their brain activation when they are deciding to do risky behaviors. (*e*) Since most of the children examined here had no (and others had only minimal) substance exposure, their brain perturbations probably did not result from substance problems. (*f*) The neural dysfunction of children with greater externalizing problems is similar to the reported dysfunction of adolescents with serious externalizing (including substance) problems. (*g*) Among these young children significant sex differences in these neural activation patterns are not apparent.

So the reviewed literature and our data strongly suggest the hypotheses that neural aberrancies reported here contribute to externalizing children's excessive real-life risk-taking, including later substance-using and antisocial choices, and further, that those neural aberrancies evolve into the aberrant neural processing known to exist in adolescents with substance use disorders and conduct disorder.

This report extends to children a growing recognition of strong neural contributions to externalizing problems. In adolescents those problems include substance use disorders, antisocial acts, and juvenile-justice involvement. The United States, more than any other country, continues placement and punitive incarceration for those problems (Hazel, 2008; Hockenberry, 2016), although incarceration actually decreases high school graduation rates and increases adult re-offending (Aizer and Doyle, 2015). We know of no evidence that such adolescents' aberrant brain function, shown here to be present in childhood, improves with punishment.

Author disclosures

Contributors

Author Crowley acknowledges: he had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design; acquisition, analysis, or interpretation of data; critical revision of the manuscript for important intellectual content: All authors.

Drafting of the manuscript: Crowley.

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Conflict of interest disclosures

During the time of this work Crowley served on the National Advisory Council of the National Institute on Drug Abuse (NIDA) and on a committee for the American Psychiatric Association's revision of its Diagnostic and Statistical Manual of Mental Disorders; both organizations reimbursed his associated travel expenses. NIDA also paid a stipend for days on which he served. Sakai received reimbursement in 2012 for completing a policy review for the Wellpoint Office of Medical Policy & Technology Assessment, Wellpoint, Inc., Thousand Oaks, CA. He also served as a member of the ARTS (a treatment program) Foundation Board until June 2015.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.drugalcdep.2017.02.028.

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