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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 desistance 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 odd-ball 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, Krangelbach 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 \geq 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.

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