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Neural activation during response inhibition is associated with adolescents' frequency of risky sex and substance use

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HIGHLIGHTS

- We evaluated response inhibition with two types of adolescent risk behavior.
- We found negative correlations between substance use and BOLD.
- This negative relationship was in the left inferior frontal gyrus (IFG) and right insula.
- We found positive correlations between risky sex and BOLD.
- This positive relationship was in the right IFG and left middle occipital gyrus.

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ABSTRACT

Objective: Introduction: While many have identified the important role of the developing brain in youth risk behavior, few have examined the relationship between salient cognitive factors (response inhibition) and different types of real-world adolescent health risk behaviors such as substance use and risky sex, within the same sample of youth.
Methods: We therefore sought to examine these relationships with 95 high-risk youth (ages 14–18; M age = 16.29 years). We examined blood oxygen level dependent (BOLD) response to an fMRI-based cognitive task designed to assess response inhibition (Go/NoGo) and past month risk behavior (number of substance use days; number of unprotected sex days).
Results: For this sample of youth, we found significant negative correlations between past month substance use and response inhibition within the left inferior frontal gyrus (IFG) and right insula (uncorrected $p < .001$; extent threshold ≥ 10 voxels). In addition, in the same contrast, we found significant positive correlations between past month risky sex and activation within the right IFG and left middle occipital gyrus (uncorrected $p < .001$; extent threshold ≥ 10 voxels).
Conclusions: These results suggest the particular relevance of these regions in this compelling, albeit slightly different, pattern of response for adolescent risky behaviors.

1. Introduction

Adolescence is a highly active developmental period. Along with numerous biological changes that take place, youthalso begin experimenting with relatively more "adult" behaviors, including substance use and sexual intercourse (Finer & Philbin, 2013). Specifically, it is during this developmental period that youth begin to make decisions about whether and when to have intercourse, and what (if any) preventive measures to take. During this same time frame, adolescents also begin to make decisions about whether or not to engage in substance use, with a large proportion experimenting with alcohol (75.6%) and cannabis (48.6%) by their senior year of high school (CDC, 2014). In contrast to patterns observed among adults who tend to favor one substance, most youth engage in polysubstance use, using both alcohol and cannabis (Moss, Chen, & Yi, 2014). Yet, despite the established clustering of sexual risk, alcohol, and cannabis use among youth (e.g., Callahan, Montanaro, Magnan, & Bryan, 2013), few studies have examined these behaviors in the same sample.

This matters because these behaviors place adolescents at higher risk for numerous negative health outcomes, including unintended pregnancy, sexually transmitted infections (STIs) (CDC, 2009), and of

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greatest concern, the human immunodeficiency virus (HIV) (Newbern et al., 2013). Unfortunately, existing prevention interventions have relatively modest effects (Bryan, Schmiege, & Broaddus, 2009; Schmiege, Broaddus, Levin, & Bryan, 2009), particularly for substance-using youth (Cooper, 2002; Tolou-Shams, Stewart, Fasciano, & Brown, 2010). Thus, it is critical to use innovative approaches to understand these relationships to guide improvements in intervention programs.

One understudied factor in this equation is the role of developmental neurocognition. We are just beginning to understand the nature of the adolescent brain and its more adaptive features (Giedd, 2012). At this time, it is well established that brain regions involved in decision-making around risk are deeply in development during this period. While the precise nature of this relationship is in debate (Mills, Goddings, Clasen, Giedd, & Blakemore, 2014; Sercombe, 2014), data suggest that adolescents' brains are particularly attuned to socio-emotional factors, including reward (Blakemore & Robbins, 2012; Galvan, 2014), while being relatively less developed in terms of cognitive control (Geier, 2013). In fact, prevailing theories of adolescent neurodevelopment, including the "dual-process" (Somerville, Jones, & Casey, 2010; Steinberg, 2010) and "triadic" models (Ernst, 2014), suggest that the relatively later maturation of the cognitive control system may be a factor in adolescent risk behavior (Bernheim, Halfon, & Boutrel, 2013; Steinberg, 2008).

1.1. Response inhibition

While several aspects of cognitive control are important in whether or not adolescents decide to engage in risk behavior (Geier, 2013), response inhibition is a particularly salient facet of this system. In practical terms, response inhibition represents an individual's ability to *not* participate in an inviting, potentially rewarding, and highly-tempting activity, even though there are compelling reasons to do so (such as not drinking at a party where alcohol is easily accessible; not using cannabis when all of one's peers are doing so; not having unprotected sex, even in the context of a rare and promising opportunity) (e.g., Crone & Dahl, 2012; Telzer, Fuligni, Lieberman, Miernicki, & Galvan, 2014). Emerging throughout adolescence, response inhibition is one of the last neurocognitive skills to develop (Tamm, Menon, & Reiss, 2002; van den Wildenberg & van der Molen, 2004; Velanova, Wheeler, & Luna, 2009). Despite the relatively delayed emergence, response inhibition is critical to successful goal achievement, as it is responsible for facilitating youths' ability to ignore and suppress irrelevant stimuli and automatic behavioral impulses (Fryer et al., 2007). Across the psychosocial literature, adolescents who have difficulties with response inhibition have greater substance-related problems, use a greater number of substances, and display greater comorbid alcohol and substance use (Nigg et al., 2006).

In the neurocognitive literature, extant work has highlighted the critical neural substrates involved in response inhibition in adolescents' real-world risk behaviors. Within neuroimaging, response inhibition is typically assessed with a Go/NoGo task. In one of the only studies of adolescent sexual risk and response inhibition, Goldenberg, Telzer, Lieberman, Fuligni, and Galvan (2013) found a positive relationship between sexual riskiness (defined on a continuous scale of contraceptive use; 1 = condom and birth control to 5 = no contraception), and blood oxygen level dependent (BOLD) response in the Go > NoGo contrast, in the superior frontal gyrus (SFG), inferior parietal lobule (IPL), insula, and MFG. They also found a significant negative correlation between sexual riskiness and neural activation (NoGo > baseline) in the superior parietal, lateral occipital, superior temporal cortex, insula, right inferior frontal gyrus (IFG), and during NoGo > Go, response in the parietal and temporal cortex, SFG, MFG, and IFG, and insula. Together, these data suggest the association between relevant frontal (SFG, MFG, IFG), parietal (IPL), and self-regulation and control regions (insula) for adolescent response inhibition and risky sex behaviors.

There have been a number of studies examining adolescent response inhibition in the context of alcohol and other substance use (Mahmood et al., 2013; Norman et al., 2011; Wetherill, Castro, Squeglia, & Tapert, 2013; Wetherill, Squeglia, Yang, & Tapert, 2013). Collectively, these studies have observed a mixed pattern, whereby some have found that youth who progress to heavy drinking evidence greater BOLD response in salient neural substrates (left angular gyrus; Mahmood et al., 2013; left MFG, right medial temporal lobe, left cerebellar tonsil; Wetherill, Castro et al., 2013), as well as less BOLD response (ventromedial prefrontal activation; Mahmood et al., 2013; right IFG, left dorsal and MF areas, bilateral motor cortex, cingulate gyrus, left putamen, bilateral middle temporal gyri, bilateral IPL; Norman et al., 2011; right IPL; Wetherill, Castro et al., 2013). Others found that transitioners to heavy alcohol use initially had lower levels of BOLD activation, but then transitioned to having relatively greater patterns of activation following initiation of alcohol use (less brain activation across bilateral MFG, right IPL, left putamen, and left cerebellar tonsil in comparison with controls, transitioning to greater activation than controls across bilateral MFG, right IPL, and left cerebellar tonsil) (Wetherill, Squeglia et al., 2013). Together, these studies highlight the relevance, if not precise directionality, between salient frontal (vmPFC, MFG), tempo-parietal (angular gyrus, temporal gyri, IPL), and striatal regions (caudate, putamen) in adolescent alcohol use and response inhibition.

The pattern appears to be less complex with cannabis. Although still relatively understudied, in line with the adolescent alcohol studies, Tapert et al. (2007) observed greater BOLD response for cannabis users (vs. non-users) on inhibition trials in the right dorsolateral PF, bilateral MF, bilateral IPL and superior PL, and right occipital gyri, along with more activation during Go trials in the right PF, insular, and parietal cortices. Others have found an absence of activation differences between adolescent cannabis users and non-cannabis using controls (Behan et al., 2014), but heightened correlations between task-activated areas for cannabis users across networks including the bilateral PL and left cerebellum.

1.2. Summary

While many have identified the important role of the developing brain in youth risk behavior, few have examined these behaviors at the same time despite their frequent co-occurrence. We therefore sought to address this gap, by directly evaluating the role of a salient cognitive factor on the frequency of adolescent unprotected sexual behavior and substance use. As one set of risk behaviors appears to have direct consequences on adolescent neurocognitive structure and function (alcohol use, cannabis use) (Feldstein Ewing, Blakemore, & Sakhardande, 2014; Lisdahl, Gilbart, Wright, & Shollenbarger, 2013), and the other (sex) does not, we were curious how neurocognitive patterns would independently compare for each of these health risk behaviors (substance use; sexual behavior) and response inhibitionin the same sample of youth. In terms of hypotheses, based on the mixed literature, we did not have *a priori* directional hypotheses, but instead posited that we would find a significant relationship between each adolescent risk behavior (frequency of unprotected sexual intercourse; frequency of substance use) and BOLD response in the middle frontal gyrus (MFG), inferior parietal lobules (IPL), and insula during the response inhibition (NoGo > Go) contrast in our fMRI-based Go/NoGo task.

2. Materials and methods

This study was a component of a larger intervention evaluation (Magnan et al., 2013). Importantly, all questions examined herein were conducted prior to youths' random assignment to intervention condition.