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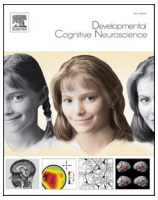

Risk-related brain activation is linked to longitudinal changes in adolescent health risk behaviors

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ABSTRACT

Middle adolescence is the period of development during which youth begin to engage in health risk behaviors such as delinquent behavior and substance use. A promising mechanism for guiding adolescents away from risky choices is the extent to which adolescents are sensitive to the likelihood of receiving valued outcomes. Few studies have examined longitudinal change in adolescent risky decision making and its neural correlates. To this end, the present longitudinal three-wave study (N_{w1} = 157, M_{w1}= 13.50 years; N_{w2} = 148, M_{w2}= 14.52 years; N_{w3} = 143, M_{w3}= 15.55 years) investigated the ontogeny of mid-adolescent behavioral and neural risk sensitivity, and their baseline relations to longitudinal self-reported health risk behaviors. Results showed that adolescents became more sensitive to risk both in behavior and the brain during middle adolescence. Across three years, we observed lower risk-taking and greater risk-related activation in the bilateral insular cortex. When examining how baseline levels of risk sensitivity were related to longitudinal changes in real-life health risk behaviors, we found that Wave 1 insular activity was related to increases in self-reported health risk behaviors over the three years. This research highlights the normative maturation of risk-related processes at the behavioral and neural levels during mid-adolescence.

Adolescence is characterized by a rise in risk-taking behavior evidenced by higher incidences of motor vehicle accidents, delinquent behavior, and substance use (Eaton et al., 2012; Steinberg, 2008). These health risk behaviors are symptoms of externalizing psychopathology that depending on their severity could index clinical disorders such as conduct disorder (Betz, 1995; Moffitt, 1993; Shaw, 2013). Prior research has documented the importance of examining problematic health risk behaviors from a developmental perspective (Moffitt and Caspi, 2001; Beauchaine, Shader, and Hinshaw, 2016) including understanding the underlying neurocognitive mechanisms of such behaviors (Blair et al., 2018). Since early onset and high frequency in health risk behaviors are associated with a host of negative health outcomes later in life (Liu, 2004; Shaw, 2013), it is critical to clarify the neural and behavioral antecedents that may contribute to the development of health risk behaviors over time.

Adolescence is also a period during which the brain undergoes significant maturation represented by structural and functional changes (Fuhrmann et al., 2015). In particular, these neurobiological changes and propensity for risk taking are believed to be especially prominent during middle adolescence (Steinberg, 2008; 2010; Casey, Jones and Hare, 2008; Shulman et al., 2016). Dual systems models suggest that the surge in problematic risk-taking behavior is the result of an imbalance in the development between neurobehavioral motivational reactive and cognitive control systems (Casey, 2015; Shulman et al., 2016). It is posited that adolescents' motivational reactive system and associated neural correlates typically found in dopaminergic mesolimbic brain areas (e.g., ventral striatum; VS) develop at a much faster rate relative to the cognitive control system (Casey, 2015; Shulman et al., 2016). While the broad ideas of various dual systems models are similar, they each make slightly different predictions regarding the age-related trajectories

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of these two systems. For instance, in Casey et al. (2008)'s dual systems model, the socioemotional system is projected to reach its maturation during mid-adolescence and plateau thereafter. This trajectory contrasts with the predictions made by the two other dual systems models (Steinberg, 2008; Luna and Wright, 2016), which posit the maturation of the socioemotional system to have an inverted-U shape. Reward responsivity in sociomotivational brain areas is thought to increase in early adolescence and decline in early adulthood. Furthermore, in the driven dual systems model proposed by Luna and Wright (2016), the cognitive control system's development is suggested to plateau in mid-adolescence instead of continuing its maturation into late adolescence (Steinberg, 2008; Casey et al., 2008). That being said, the general suppositions of these neurodevelopmental models are similar in that they involve a mismatch in the ontogenic development of two brain systems (socioemotional and cognitive control). It is also important to note that middle adolescence is proposed to be a critical period in the maturation of the socioemotional system (Steinberg, 2008; Casey et al., 2008; Luna and Wright, 2016) and cognitive control system (Luna and Wright, 2016). Across dual systems models, middle adolescence is the period during which the developmental mismatch in these neural systems is at its greatest representing a neurobiological vulnerability for risk taking behavior (Steinberg, 2008; Casey et al., 2008; Luna and Wright, 2016; Shulman et al., 2016).

However, this theoretical framework may be too simplistic, and the reality is likely more complex and may involve other brain networks that contribute to risky decision-making. For instance, the triadic model of adolescent behavior (Ernst, Pine, and Hardin, 2006) posits that adolescent risky behavior may be the result of dynamic interactions between three functional brain systems: 1) approach/reward system; 2) avoidance system; and 3) regulatory system. The imbalance in the recruitment of these brain networks during decision making is thought to drive adolescent risk taking. In particular, the triadic model posits that some adolescents may recruit brain areas involved in avoidance and regulatory controls such as the insular, dorsolateral prefrontal, and anterior cingulate cortices to a lesser extent relative to approach/reward brain areas (e.g., VS), resulting in heightened risk taking.

Combining this neurodevelopmental framework with prior work on value-based decision making (Rangel, Camerer, and Montague, 2008), it is well known that individuals consider not only the rewards per se but also the potential likelihood of receiving such rewards or *risk*. A key element shared across a myriad of problematic health risk behaviors is that the consequences of choices are often uncertain, and individual preferences toward risk have been shown to predict decision making behavior. Specifically, decision-making research has shown that both adolescents and adults process risk, usually defined as the variance of potential outcomes, in the bilateral insular cortex (Kuhnen and Knutson, 2005; Mohr et al., 2010; Platt and Huettel, 2008; Preuschoff et al., 2008; van Duijvenvoorde et al., 2015; Xue et al., 2009). The magnitude of activation in risk-related brain areas may reflect the degree to which an individual engages in risky decisions and may demonstrate an individual's preference for choosing (or not choosing) risky options (Xue et al., 2009; Platt and Huettel, 2008). Insular cortex activation is consistently associated with risk-averse behavior in both adolescents and adults, suggesting the insular cortex may help guide individuals away from risk-taking (Xue et al., 2009; Platt and Huettel, 2008; Paulus et al., 2003; Mohr et al., 2010; van Duijvenvoorde et al., 2015; Paulsen et al., 2011). Adolescents, in particular, have been shown to exhibit hyperactivity of the insular cortex (van Duijvenvoorde et al., 2015), and activity in this brain region is shown to be predictive of adolescent health risk behaviors (Kim-Spoon et al., 2016). Moreover, patients with lesions to their insular cortex show greater risk taking and fail to adapt their choices based on the likelihoods of winning in comparison to a control group (Clark et al., 2008). This finding is in alignment with the extensive neuroimaging literature demonstrating that the insular cortex is critical for signaling the likelihood of receiving potentially negative outcomes. Using a value-based decision-making approach, we conceptualize behavioral risk sensitivity as a preference that guides individuals toward (risk-seeking) or away (risk-aversion) from choosing risky options. This framework allows us to elicit and measure behavioral risk sensitivity based on the decisions in an economic lottery choice task. Neural risk sensitivity is defined as the recruitment of brain areas typically involved in processing risk information such as the insular cortex with greater activation in these risk-related brain areas representing higher levels of risk processing.

In terms of links between adolescent risky behavior and externalizing psychopathology, understanding the neurodevelopmental trajectory of risk processes at the behavioral and neural levels would help to identify neurobehavioral phenotypes that serve as precursors for predicting which adolescents may be more susceptible to negative health outcomes. In line with the ontogenic process model of externalizing psychopathology (Beauchaine, Shader, and Hinshaw, 2016), adolescents may exhibit individual vulnerabilities in the form of blunted *sensitivity to risk* at the behavioral and neural levels which may predispose them to engagement in problematic health risk behaviors leading to negative health outcomes. Furthermore, a key aspect in the ontogenic process model of externalizing psychopathology is that the development of these individual vulnerabilities (such as individual risk sensitivity) should be examined over time. Currently, a gap in the current literature remains regarding how behavioral risk sensitivity and neural risk sensitivity develop during adolescence and prospectively contribute to the development of risky behaviors. This is important to address because identification of potential neurobiological and behavioral vulnerabilities early on during adolescence may be meaningful predictors of developing externalizing psychopathology or changes in health risk behaviors over time. For instance, does greater neural or behavioral sensitivity to risk during early adolescence predict inter-individual changes in health risk behaviors over time?

To date, much knowledge regarding developmental differences in risk preferences relies on cross-sectional work comparing age groups. While cross-sectional designs are practical, they provide snapshots at a given point in time. Most prior adolescent decision-making studies include a wide range of age groups, often inconsistent, making it difficult to draw inferences regarding developmental patterns. Longitudinal studies instead investigate intra-individual change across time which is better suited to study developmental processes (Baltes and Nesselroade, 1979). Another advantage of a longitudinal approach is examining whether earlier measures are related to (changes in) future behavior. Identifying predictors of risk-taking behavior is critical for determining which adolescents may be most vulnerable for maladaptive risk-taking later in life. In the risky decision-making neuroimaging literature, the use of longitudinal whole-brain analyses is rare. This possibly prevents an accurate characterization of neurobiological function (Friston et al., 2006). Examining whole-brain responses over time might provide a more comprehensive picture of the neural regions involved in risk information processing and their change over time.

In the present study, we longitudinally examined how neurobehavioral risk sensitivity changed during middle adolescence (Wave 1: 13–14 years old; Wave 2: 14–15 years old; Wave 3: 15–16 years old) when vulnerability to risk-taking is at its greatest (Burnett et al., 2010; Dahl, 2004; Steinberg, 2008). We focus on middle adolescence because it is the period during which the imbalance of neurodevelopmental systems of risky behavior is hypothesized to be at its highest as well as the stage when youth begin to accelerate engagement in risk taking behaviors (Willoughby et al., 2014; Jones et al., 2020; Eaton et al., 2012). First, we characterized the maturation of behavioral risk sensitivity measured using an economic lottery choice task across mid-adolescence. Based on prior studies using different measures of behavioral risk sensitivity (Asscheman et al., 2020; van Duijvenvoorde et al., 2015), we hypothesized that adolescents would make less risky choices across the three years, reflecting greater behavioral risk sensitivity (i.e., risk aversion). Second, we take advantage of statistical advancements in functional magnetic resonance imaging (fMRI) to assess

longitudinal changes in neural risk sensitivity at the whole-brain level (Chen et al., 2013; Guillaume et al., 2014; Skup, 2010). To estimate intra-correlations between time points for a given participant, fitting standard linear random-effects models to neuroimaging data is computationally intensive, and it creates issues with non-convergence. To solve these issues, we leveraged a non-iterative sandwich estimator (Guillaume et al., 2014) to analyze longitudinal changes in neural risk sensitivity over time using this longitudinal approach. To investigate brain-behavior relationships in risk sensitivity, we tested whether longitudinal changes in risk-related processing in the adolescent brain were related to changes in behavioral risk sensitivity over time. Based on prior research (Lauharatanahirun et al., 2018; Kim-Spoon et al., 2016; Maciejewski et al., 2018; Asscheman et al., 2020; Li et al., 2019; Paulsen et al., 2011; Mohr et al., 2010; van Duijvenvoorde et al., 2015), we hypothesized greater risk-related activation in the insular cortex in response to risky options. We hypothesized that greater risk-related activation would be related to risk-averse behavior in the economic lottery choice task (Li et al., 2019; Asscheman et al., 2020). Third, we examined whether baseline (Wave 1) individual differences in risk sensitivity at the behavioral and neural level were related to changes in self-reported health risk behaviors across three years. Specifically, we tested whether baseline insular risk-related processing was related to changes in health risk behaviors given the literature implicating the insular cortex as a region critical to risk processing (Mohr et al., 2010; van Duijvenvoorde et al., 2015). We hypothesized that lower baseline insular risk-related brain activation would be related to greater longitudinal increases in health risk behaviors across the three years.

1. Method

1.1. Participants

Adolescents participated in a longitudinal study that spanned the critical period of middle adolescence, ages 13–16 (Wave 1: 13–14 years old; Wave 2: 14–15 years old; Wave 3: 15–16 years old), during which increases in risk-taking behaviors are likely to occur (Dahl, 2004; Steinberg, 2008). A total of 167 mid-adolescents (48% female, 78% White) from the southwest Virginia area participated in an ongoing longitudinal study. In terms of socioeconomic status, median annual household income ranged from $35–000-$50,000 for all time points (consistent with the median for the region; United States Census Bureau, 2010), ranging from less than $1000 to greater than $200,000 per year. Among parents of our sample, 34% had a high school degree or less, 24% some college education, 24% bachelor's degree, and 18% reported having a graduate degree. Mid-adolescent participants at Wave 1 were starting and still physically developing based on the Pubertal Development Scale (PDS, Peterson et al., 1988; M =.28, SD =.52) that assesses the physical development for youth under the age of 16. Inclusion criteria consisted of being 13 or 14 years old at Wave 1, a native English speaker, and having vision corrected to see the computer display. Exclusion criteria consisted of the following: claustrophobia, history of head injury resulting in loss of consciousness for more than 10 min, orthodontia impairing image acquisition, severe psychopathology (e.g., psychosis), and other magnetic resonance contraindications (e.g., pacemaker, aneurysm clips, neurostimulators, metal in eyes, cochlear implants or other implants). All exclusion criteria were assessed through self-report. The final sample at Wave 1 included 157 adolescents (48% female) with a mean age of 13.51 years (SD=0.50). At Wave 2, the final sample included a total of 148 adolescents (47% female) with a mean age of 14.51 years (SD=0.50). At Wave 3, the final sample included a total of 143 adolescents (48% female) with a mean age of 15.57 years (SD=0.52). For the prospective longitudinal growth curve model analyses, we included data from adolescents who had imaging data at Time 1 (N = 144; see Supplementary Table 4 for detailed information on Exclusions at each Wave). For whole-brain longitudinal fMRI analyses, we used a subset of the data that included participants who had data for all three time points (N = 103). Adolescent participants completed all study assessments within the same session at each time point. All participants were given instructions for the lottery choice task, and they engaged in a practice session of six trials to ensure comprehension of the task. Adolescents were recruited via flyers, recruitment letters, e-mail, and word of mouth. All participants and parent(s) of the participants provided written informed assent/consent in line with Virginia Tech Institutional Review Board guidelines.

1.2. Measures

1.2.1. Economic lottery choice task

Adolescents made choices between pairs of risky gambles at each time point in an adapted lottery choice task (Holt and Laury, 2002; Fig. 1A). Participants completed the task while simultaneously monitoring their blood-oxygen-level-dependent (BOLD) response using functional magnetic resonance imaging (fMRI). Each gamble option included a high and low monetary outcome with an associated probability of occurring. A pie with ten slices represented probabilities, in which each piece corresponded to ten percent. Each pair of gambles included one option that was riskier than the other. Risk was calculated using a scale-free measure of variance, coefficient of variation (CV). CV is computed by dividing the standard deviation of potential outcomes by the option's expected value (EV; Weber, Shafir, and Blais, 2004).

$$EV = P_{high} * V_{high} + P_{low} * V_{low}$$

$$CV = \frac{\sqrt{P_{high}(V_{high} - EV)^2 + P_{low}(V_{low} - EV)^2}}{EV}$$

P_{high} and P_{low} indicate the probability of receiving the high and low outcomes, respectively, while V_{high} and V_{low} correspond to the high and low monetary outcomes. Prior work shows neural correlates of outcome distributions to be more sensitive to representations scaled by distribution mean rather than in an absolute manner (Bach, Symmonds, Barnes and Dolan, 2017; McCoy and Platt, 2005; Weber, Shafir and Blais, 2004). CV also allows comparing risk sensitivity across different scales or outcome dimensions (Weber, Shafir and Blais, 2004). Since probabilities were the same for both gambles in a given trial, the difference between low and high monetary amounts differentiated the level of risk between options. That is, the option with the smaller difference in monetary outcomes (e.g., $1.88 - $1.50 = 0.38, Fig. 1A) indicates relatively low risk compared to the option with the larger difference in outcomes (e.g., $3.61 - $0.09 = 3.52, Fig. 1A). Low-risk options had CV values that ranged from 0.07 to 0.28, while high-risk options ranged from 0.52 to 3.07. Outcomes and probabilities randomly varied across trials. Adolescents were instructed that each trial was independent of other trials and was equally likely to be selected for compensation. Participants received bonus compensation based on the actual results from five randomly selected trials. The task comprised 72 trials and took approximately 30 min to complete.

Our experimental design was based on previous study designs optimized for examining decision-related neural responses (van Leijenhorst et al., 2006, 2008, 2010). In this task, adolescents were shown the pair of gamble options and given a fixed four seconds to decide. Participants used a magnetic resonance compatible button box to make their selections. Next, adolescents saw a fixation cross with one to three seconds jitter. Following the fixation cross, participants saw the results of their choice for a fixed period of two seconds.

1.2.2. Health risk behaviors (HRBs)

Adolescent health risk behaviors were measured at each wave (1, 2, and 3) using adolescents' responses on a subset of items from the Things I Do questionnaire (Conger et al., 1994) that were consistent with the Centers for Disease Control's definition of adolescent risk behavior (Eaton et al., 2012; Kann et al., 2016), including rule-breaking and

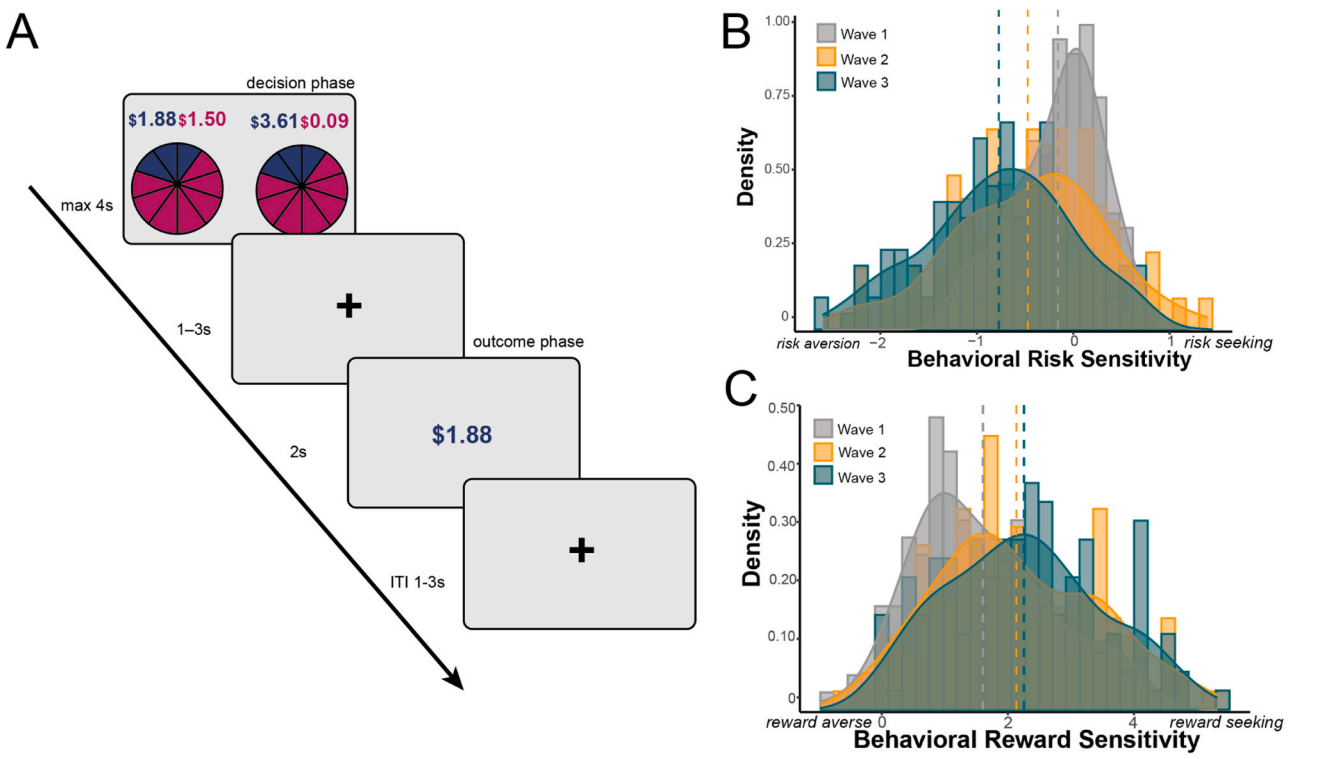

Fig. 1. A) Adolescents made 72 decisions between pairs of risky gambles in an economic lottery choice task (Holt and Laury, 2002). Each gamble consisted of a high and low monetary outcome with an associated probability. Outcomes and probabilities were represented with corresponding colors (pink and blue). The time course of a given trial included a decision phase followed by a jittered fixation interval and an outcome phase, in which participants were shown the results of their choice followed by a jittered inter-trial interval (ITI). B) Distribution of behavioral risk sensitivity scores within each wave, where lower values indicate greater risk aversion. The dotted lines represent the mean. C) Distribution of behavioral reward sensitivity scores within each wave. Higher values indicate greater reward seeking. The dotted lines represent the mean.

violent behaviors and alcohol, tobacco, and other drug use which represent problematic externalizing behaviors that are risk factors for developing externalizing psychopathology. Examples of the final 12 items include "Smoked a cigarette or used tobacco" and "Drunk a bottle or glass of beer or other alcohol." Adolescents responded to items indicating the frequency of behavior as, "0 = not at all", "1 = once or twice", or "2 = more than twice". Higher scores on this measure indicated higher risk-taking. The HRB composite showed acceptable reliability at Wave 1 (α = .68), Wave 2 (α = .74), and Wave 3 (α = .80).

1.2.3. Intelligence

At Time 1, adolescents' verbal intelligence was measured using the Kaufman Brief Intelligence Test (2nd Edition, KBIT; Kaufman and Kaufman, 2014). KBIT is a widely used intelligence assessment used for children and adults. The KBIT-2 verbal intelligence measure is also strongly correlated with other comprehensive measures such as the Wechsler Adult Intelligence Scale (3rd Edition, WAIS-3; Wechsler, 1997, Walters and Weaver, 2003). Intelligence was used as a covariate, given that it has been shown to relate to decision-making behavior (Flouri, Moulton, and Ploubidis, 2019).

2. Statistical analyses

2.1. Behavioral analysis

Behavioral data from the lottery choice task was analyzed using a generalized logistic linear mixed-effects model using the lme4 package in R (Bates, Mächler, Bolker, and Walker, 2014). Our primary variable of interest in this analysis was risk sensitivity. Risk sensitivity was defined as the difference between the *CV* of the high and low-risk options ($CV_{high} - CV_{low}$). Reward sensitivity was defined as the difference between the *EV* of the high and low-risk options ($EV_{high} - EV_{low}$). Since our focus in this study was to examine longitudinal changes in risk sensitivity, reward sensitivity was included as a covariate in our mixed-effects models. An additional predictor of wave represented the year during which adolescents completed the lottery choice task. It is important to note that reward sensitivity in the present study refers to differences in the *objective* rather than subjective, expected values between options. The dependent variable was the likelihood of either choosing the safer (coded as 0) or riskier (coded as 1) gamble. Additional covariates of gender and intelligence as measured by the Kaufman Brief Intelligence Test were included.

The model is formally described as:

Level 1:

$$\text{logit}\,(y_{it}) = \pi_{0i} + \pi_{1i}*\text{Risk}_{it} + \pi_{2i}*\text{Reward}_{it} + \pi_{3i}*\text{Wave}_{it} + \pi_{4i}*(\text{Risk}_{it}*\text{Wave}_{it}) + \pi_{5i}*(\text{Reward}_{it}*\text{Wave}_{it}) + \varepsilon_i$$

Level 2:

$$\pi_{0i} = \beta_{00} + \beta_{01}*\text{Gender} + \beta_{02}*KBIT\ Verbal + \xi 0i$$

$$\pi_{1i} = \beta_{10}$$

$$\pi_{2i} = \beta_{20}$$

$$\pi_{3i} = \beta_{30}$$

$$\pi_{4i} = \beta_{40}$$

$$\pi_{5i} = \beta_{50}$$

y_{it} is the response of the i participant at the t trial, in which $y_{it} = 0$ indicates choosing the low-risk gamble and $y_{it} = 1$ indicates choosing the high-risk gamble. Between-subject variance is captured by the random effect ξ, which accounts for the repeated-measures nature of

the data. Within-subject variance is captured by the random effect, ε. Fixed effects are represented by the parameter, β. All independent variables in the model were mean centered, in which β_{00} indicates the average likelihood of choosing to take the high-risk gamble for mean risk and reward. Main effects of risk, reward, and wave are represented by β_{10}, β_{20}, and β_{30}, respectively. Interaction effects of risk and reward by wave are represented by β_{40} and β_{50}, respectively. Positive values of risk sensitivity indicated a greater likelihood of choosing the high-risk gamble when the difference between CV_{high} and CV_{low} is large (i.e., lower risk sensitivity). Negative values indicate a greater likelihood of choosing the low-risk gamble when the difference between CV_{high} and CV_{low} is small (i.e., higher risk sensitivity). Positive values of reward sensitivity indicated a greater likelihood of choosing the high-risk gamble when the difference between EV_{high} and EV_{low} is large (i.e., increasing expected payoff). Negative values indicated a greater likelihood of choosing the low-risk gamble when the difference between EV_{high} and EV_{low} is small (i.e., decreasing expected payoff). To examine the extent to which individual differences in risk sensitivity exist within wave, a separate mixed-effects model was analyzed for each wave that followed the model above except the following predictors: wave, risk * wave, reward * wave.

2.2. fMRI acquisition

fMRI data were acquired using a 3 T Siemens Tim Trio scanner with a twelve-channel head matrix coil. Anatomical images were collected using a high-resolution magnetization prepared rapid acquisition gradient echo sequence with the following parameters: TR = 1200 ms, TE= 2.66 ms, field of view (FoV) = 245x245mm, and 192 slices with the spatial resolution of 1 × 1 x 1 mm. Functional images were obtained using the following parameters: slice thickness = 4 mm, 34 axial slices, FoV= 220 × 220 mm, repetition time = 2 s, echo time = 30 ms, flip angle= 90 degrees, voxel size = 3.4 × 3.4 × 4 mm, 64 × 64 grid, and slices were hyper-angulated at 30º from anterior-posterior commissure.

2.2.1. Longitudinal changes of risk processing

Analysis of neuroimaging data was conducted using SPM8 and the Sandwich Estimator toolbox for longitudinal fMRI data (SwE; Guillaume et al., 2014). Preprocessing of imaging data was performed using the following procedure: data were corrected for excessive head motion using a six-parameter rigid body transformation and realigned, mean functional image was co-registered to the anatomical image, the anatomical image was segmented, functional volumes were normalized and registered to the Montreal Neurological Institute (MNI) template, and then smoothed using a 6 mm full-width-half-maximum Gaussian filter.

Whole-brain general linear model analysis was conducted to assess neural computations of risk in the adolescent brain. For each subject, decision phase BOLD responses were modeled with a boxcar function representing the length of time it took each participant to make a choice. Outcome phase BOLD responses were modeled with a duration of two seconds. The model included two parametric regressors modulating decision phase activation corresponding to the CV of chosen options and EV of chosen options. A parametric regressor at the outcome phase indicating whether the subject received the high or low monetary outcome was also included in the model. All regressors included in the model were convolved with a canonical hemodynamic response function. Here, the parametric regressor of interest was the CV of chosen options. The EV of chosen options was included as a covariate of no interest in line with our behavioral analysis. Also, six motion parameters were included in the subject-level model as covariates of no interest.

Subject-level contrasts for the regressor of interest – CV of chosen options (i.e., risk processing) – were entered into a group-level model using SwE to assess the change in neural risk processing across time and the average effect of neural risk processing over time. In contrast to our previous studies (Asscheman et al., 2020; Kim-Spoon et al., 2016; Lauharatanahirun et al., 2018; Li et al., 2019; Maciejewski et al., 2018), we used SwE to adequately account for the repeated-measures structure of the data by implementing the sandwich variance estimator (Guillaume, Hua, Thompson, Waldrop, & Nichols, 2014). For group-level regression analyses, individual estimates of behavioral risk sensitivity were split into a cross-sectional (time-invariant) and longitudinal (time-varying) component following the procedure outlined in Guillaume et al. (2014). While previous work from our group has examined risk-related processing (Asscheman et al., 2020; Lauharatanahirun et al., 2018), our approach in the current study allowed for a whole-brain longitudinal assessment of the following: i) the relation between average neural risk processing and average behavioral risk sensitivity across all three time points, and ii) the relation between change in neural risk processing across time and change in behavioral risk sensitivity across time. All neuroimaging results used a false discovery rate (FDR) multiple comparisons correction with a threshold of $p < .05$.

2.3. Longitudinal prediction of health risk behaviors

2.3.1. Neural risk sensitivity at wave 1

We used a functional ROI approach based on whole-analysis to assess whether insular risk-related brain activation at baseline would predict longitudinal changes in health risk behaviors across middle adolescence. Specifically, we functionally defined the left and right insular cortices based on neural responses that were parametrically modulated by the CV of chosen options at Wave 1 within a whole-brain analysis. Eigenvariate values were extracted from these functionally defined ROIs and used in subsequent latent growth curve model analysis. This method allowed us to assess whether insular activation at an earlier period of adolescence is a precursor for changes in health risk behaviors later on during adolescence. For our exploratory LGCM analyses examining other risk-related brain regions (left and right ventral striatum and anterior cingulate cortex), we could not take the functional ROI approach since these regions were all part of the same cluster. To differentiate these regions, we extracted eigenvariate values of the peak voxel coordinates (left VS [−9, 2, −5]; right VS [12 2 −5]; and anterior cingulate cortex [3 35 22]) for these regions using a 6 mm sphere.

2.3.2. Latent growth curve model (LGCM)

To test whether behavioral and neural indices of risk sensitivity predicted the development of health risk behavior across the three waves, we fitted latent growth curve models (LGCM) in *R* (version 4.0.2; R Core Team, 2013) using the package *lavaan* (version 0.6–8; Rosseel, 2012). In LGCM, developmental trajectories are captured by two latent factors – the intercept (i.e., starting level) and the slope (i.e., change across time-points). First, we examined whether there were significant changes in health risk behaviors over time using an unconditional LGCM (i.e., without covariates). We then moved to a conditional LGCM, where the intercept and slope were regressed on insula activation. Although the focus of the present study was specific to insular activation and health risk behaviors, additional exploratory LGCM analyses were conducted to assess whether other risk-related brain areas (left and right VS, anterior cingulate cortex) identified in the whole brain analysis were also related to changes in health risk behaviors. Gender and intelligence were added as covariates to the conditional LGCM. We used full information maximum likelihood estimation (FIML) to control missing data. Model fit was evaluated using the Tucker–Lewis Index (TLI), the Comparative Fit Index (CFI), and the Root Mean Square Error of Approximation (RMSEA). For the TLI and CFI, values between .90 and .95 are considered acceptable (Bollen and Curran, 2006), and values of .95 and greater as good (Hu and Bentler, 1999). For the RMSEA, adequate models have values of .08, and values below .06 are considered good (Browne and Cudeck, 1992). As a robustness check, we conducted an additional analysis in which the behavioral risk sensitivity at Wave 1 was included as a covariate in the model. Outliers (values outside 1% and 99% percentile) were winsorized before analyses to retain statistical

power and attenuate bias resulting from elimination (Ghosh and Vogt, 2012).

3. Results

Before conducting longitudinal analyses, we examined intercorrelations among our variables of interest: behavioral risk sensitivity, neural risk processing, and adolescent health risk behaviors (see Table 3). We observed a negative correlation between behavioral risk sensitivity at Wave 1 and bilateral insular risk-related activation at Wave 1 (r_{right}=−.26, r_{left} =−.25, see Table 3). Higher levels of insular risk-related activation at Wave 1 were related to lower behavioral risk sensitivity (i.e., more risk averse behavior in the task). There were no significant associations between insular risk-related activation (right or left) at Wave 1 with health risk behaviors at any of the three time points (*r* range: −.002 to.06, *ps* > .06, see Table 3). However, we did observe a significant positive correlation between behavioral risk sensitivity at Wave 1 with health risk behaviors at Waves 2 (r = .22, see Tables 3) and 3 (r = .19, see Table 3). Greater risk seeking behavior in our experimental task at Wave 1 was associated with engagement in higher levels of adolescent health risk behaviors in later years during middle adolescence. We did not observe a concurrent significant association between behavioral risk sensitivity and health risk behaviors at Wave 1 (r = .03, see Table 3).

3.1. Longitudinal changes in risk sensitivity

On average, adolescents chose the high-risk gamble 46% at Time 1 (*SD* = 0.16), 40% at Time 2 (*SD* = 0.18), and 36% at Time 3 (*SD* = 0.16). Logistic linear mixed-effects analysis showed that when the difference in riskiness between gamble options was high, adolescents displayed a decreased likelihood of selecting the high-risk gamble on average (Table 1; Fig. 1B). On the other hand, when the difference in expected reward between gamble options was high, adolescents showed an increased likelihood of choosing the high-risk option on average (Table 1; Fig. 1C). There was also a significant main effect of wave, which indicates that adolescents became less likely to choose the high-risk option over time (see Table 1). A significant Risk Sensitivity * Wave interaction was found, showing that adolescents as a group exhibited greater risk sensitivity (i.e., more likely to choose the low-risk option) over time (Table 1). A significant Reward Sensitivity * Wave interaction was also found, which showed that adolescents were more likely to choose options with a higher expected monetary reward over time (Table 1).

We conducted follow-up tests to examine whether the effects of risk and reward on choice behavior were present within each wave. Indeed, adolescents showed main effects of risk (see Table 2) and reward (see Table 2) on risky choice behavior. In addition, we examined the extent to which inter-individual rank-order stability in behavioral risk sensitivity was observed across the three time points. Clarifying whether adolescent inter-individual differences in behavioral risk sensitivity are stable provides information regarding when these preferences may be more flexible and potentially susceptible to change. Interestingly, the stability in individual differences in risk sensitivity were stronger over time, as evidenced by a significantly lower positive Wave 1 and Wave 2 correlation (r = .39, 95% CI [.33,.59], p < .001) relative to a higher positive correlation between Wave 2 and Wave 3 (r = .54, 95% CI [.41,.65], p < .001; Fisher's z = −1.68; p = .04). In contrast, adolescents exhibited consistent stability in reward sensitivity over time as evident by no significant differences in between-wave correlations ($r_{w1\&w2}$ =.47, 95% CI [.33,.59] p < .001; $r_{w2\&w3}$ =.47, 95% CI [.33,.59], p < .001; Fisher's z = −.04, p = .48).

3.2. Neuroimaging

To conduct whole-brain group-level longitudinal analyses, we used the sandwich variance estimator (SwE, Guillaume et al., 2014) which assumes that each subject within a group shares the same session-based covariance structure. The sandwich estimator toolbox for longitudinal fMRI data does not require individual dummy variables to be estimated, and instead only a population model is estimated using an Ordinary Least Squares method (Guillaume et al., 2014). This approach both reduces computational load and convergence failures that often occur with complex mixed-effects models. Using the sandwich estimator toolbox (Guillaume et al., 2014), we conducted whole-brain group-level analyses to test for parametric effects of risk during the decision phase of the task controlling for parametric effects of reward. Whole-brain group-level analyses revealed significant hemodynamic responses correlated with parametrically increasing CV for chosen options in the bilateral insular cortex, medial prefrontal cortex (especially dorsal anterior cingulate cortex), and bilateral ventral striatum (see Fig. 2, Supplementary Table 1). Moreover, imaging analyses revealed a significant linear change in the encoding of risk across the three waves such that increased activation was observed in the insular cortex, bilateral anterior cingulate cortex, right pallidum, right thalamus, and right superior orbitofrontal cortex for increasing risk over time (see Fig. 3, Supplementary Table 2). Here, we show that similar to behavioral risk sensitivity, neural correlates of risk linearly increase over time showing that the brain is becoming more sensitive to high-risk options. Next, we were interested in examining the extent to which average behavioral risk sensitivity was related to average neural risk processing across the three waves. We conducted a multiple regression analysis on the parametric contrast of CV using risk sensitivity estimates from our within-wave analyses as a second-level regressor in the model, which also included six movement regressors as covariates. Our analysis revealed that greater risk sensitivity (i.e., risk aversion) was significantly related to increased parametrically modulated risk activation of the bilateral insular cortex, bilateral anterior cingulate cortex, left pallidum, and right caudate (see Fig. 4, Supplementary Table 3). That is, greater risk aversion averaged across all waves was related to greater activation in brain areas associated with risk-related processing on average across all waves.

3.3. Prediction of health risk behaviors

Table 3 summarizes the descriptive statistics and correlations

Table 1
Logistic Linear Mixed-Effects Model for Adolescent Behavioral Risky Choice on Risk Sensitivity, Reward Sensitivity, and Wave.

	B	*95% CI*	*SE*	*Z*	*β*	*p*
Intercept	0.42	[− 0.69, 1.53]	0.57	0.74	0.43	0.45
Risk Sensitivity	**-0.21**	**[− 0.28, − 0.13]**	**0.04**	**-4.60**	**–0.12**	**< .001**
Reward Sensitivity	**0.73**	**[0.71, 0.74]**	**0.01**	**36.94**	**1.14**	**< .001**
Wave	**-0.36**	**[− 0.37, − 0.34]**	**0.01**	**-19.79**	**–0.36**	**< .001**
Gender	-0.15	[− 0.44, 0.14]	0.15	-1.03	–0.15	0.29
KBIT Verbal	-0.01	[− 0.02,.009]	0.01	-0.91	–0.01	0.36
Risk Sensitivity*Wave	**-0.60**	**[− 0.75, − 0.44]**	**0.08**	**-6.77**	**–0.19**	**< .001**
Reward Sensitivity* Wave	**0.23**	**[0.15, 0.30]**	**0.04**	**5.32**	**0.15**	**< .001**

Note. Significant associations are indicated in bold.

Table 2
Logistic Linear Mixed Effects Model for Adolescent Behavioral Risky Choice on Risk Sensitivity and Reward Sensitivity within Each Wave.

	Wave 1					*Wave 2*					*Wave 3*				
	B	*95% CI*	*SE*	*Z*	*β*	*p*	*B*	*95% CI*	*SE*	*Z*	*β*	*p*	*B*	*95% CI*	*SE*	*Z*	*β*	*p*
Intercept	0.58	[− 0.59,1.75]	0.60	0.96	0.56	0.33	0.44	[− 1.22, 2.10]	0.85	0.51	0.44	.60	-0.92	[− 2.52,0.68]	0.82	-1.11	–0.92	.26
Risk Sensitivity	**–0.31**	**[− 0.50, − 0.11]**	**0.10**	**-3.03**	**–0.17**	**.002**	**-0.91**	**[− 1.20, − 0.61]**	**0.15**	**-5.82**	**–0.50**	**< .001**	**-1.59**	**[− 1.23, − 1.94]**	**0.18**	**-8.84**	**–0.88**	**< .001**
Reward Sensitivity	**1.09**	**[− 0.95,1.22]**	**0.07**	**15.16**	**1.69**	**< .001**	**1.45**	**[1.29, 1.60]**	**0.08**	**16.43**	**2.26**	**< .001**	**1.57**	**[1.39,1.74]**	**0.09**	**17.06**	**2.44**	**< .001**
Gender	-0.17	[− 0.44, 0.10]	0.14	-1.21	–0.17	0.22	-0.31	[− 0.70,0.08]	0.20	-1.51	–0.31	.13	0.19	[− 0.20,0.58]	0.20	0.97	0.19	.33
KBIT Verbal	-0.01	[− 0.02,0.009]	0.01	-1.12	–0.01	0.25	-0.02	[− 0.03, − .0004]	0.01	-1.32	–0.02	.18	-0.01	[− 0.02,0.009]	0.01	-0.63	–0.01	.52

Note. Significant associations are indicated in bold.

between the study variables included in the LGCM including the exploratory LGCM analyses we conducted for other risk-related brain regions (i.e., left ventral striatum, right ventral striatum, and anterior cingulate cortex). Table 4 summarizes the unconditional and conditional LGCMs. All models showed a good fit to the data. Results showed that there was a significant increase in health risk behaviors from Wave 1 to Wave 3, with significant variation around the intercept and slope, indicating that adolescents differed from each other in their starting level and amount of change of health risk behaviors over time.

When examining the functionally defined ROIs of the left and right insular cortices as predictors of health risk behaviors, we found that the right insular cortex, and not the left, was associated to changes in health risk behaviors over time (see Table 4). Results showed that the right insular cortex (and no other risk-related brain regions) was negatively associated with the change in health risk behaviors (i.e., slope; see Table 4, Fig. 5), but it was not associated with the intercept of health risk behaviors (see Table 4). This finding indicates that less risk-related activation in the right insular cortex at Wave 1 was related to steeper increases in health risk behaviors over a three-year period. When adding the behavioral risk sensitivity at Wave 1 as a covariate, the association between activation in the right insular cortex with the slope of health risk behavior remained in the same direction but became non-significant s (Table 5). Behavioral risk sensitivity at Wave 1 was significantly related to changes in health risk behaviors over time, after controlling for the effects of insular activation, such that greater risk taking during the task at Wave 1 predicted increases in health risk behaviors over the three-year period (Table 5). No significant association was found between behavioral risk sensitivity at Wave 1 and the intercept of health risk behaviors (Table 5).

4. Discussion

The purpose of the present study was to longitudinally investigate how risk sensitivity at the behavioral and neural levels develop during middle adolescence, an age range noted for its substantial neurobiological growth as well as high potential for risk taking (Casey et al., 2008; Dahl, 2004; Steinberg, 2008; Shulman et al., 2016). Middle adolescence is also a time when adolescents first observe and initiate health risk behaviors (Jones et al., 2019; Eaton et al., 2012). For instance, national survey data from the United States indicate that the majority of adolescents will likely engage in some form of substance use during high school (U.S. Department of Health and Human Services, 2020). Importantly, we investigated whether individual differences in sensitivity to risk information either at the behavioral or neural level can be used to predict which adolescents may be more susceptible to future health risk behaviors. First, our findings demonstrate that behavioral risk sensitivity significantly changed during middle adolescence such that adolescents become more risk averse as they become older. This finding aligns with cross-sectional (e.g., Tymula et al., 2013) and longitudinal (Asscheman et al., 2020) studies that examine developmental changes in risk preferences, indicating increasing risk avoidance during middle adolescence. It is essential to point out that prior studies, including work from our group (Asscheman et al., 2020), used different risk sensitivity measures from economic choice tasks relative to those used in the current study. Moreover, our finding that adolescents become more risk averse as they become older is consistent with prior research examining the trajectory of self-reported risk perceptions (Blankenstein et al., 2021) and risk-taking behaviors (Duell et al., 2018) across a broader age range and across several countries (Duell et al., 2018). We also examined the unique contributions of behavioral and neural risk sensitivity beyond reward sensitivity in both behavioral and neural levels analyses; prior work has shown that both potential risks and rewards contribute to risky decision making (van Duijvenvoorde et al., 2015). We replicated previous research results using the difference between the *CV* of the high and low-risk options ($CV_{high} - CV_{low}$), speaking to the robustness of our results. Second, adolescents' neural

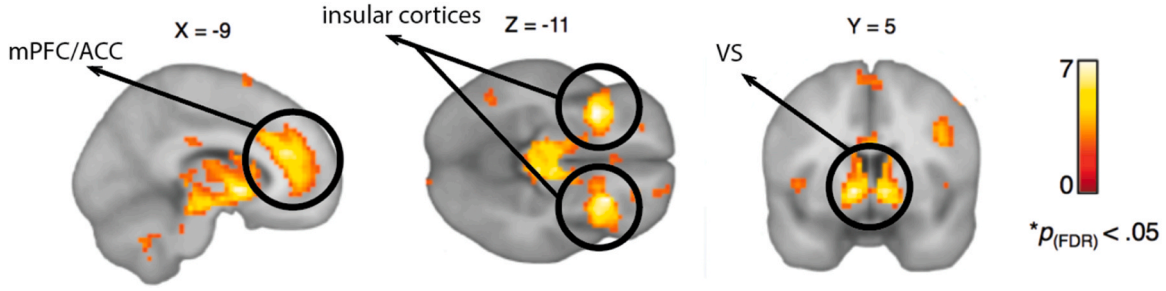

Fig. 2. *Mean Neural Response to Increasing Risk during the Decision Phase Across Waves.* Using a longitudinal whole-brain group analysis, mean neural responses to parametrically increasing coefficient of variation (CV, i.e., risk) for chosen options were identified in the medial prefrontal cortex (mPFC; especially the anterior cingulate cortex, ACC), bilateral insular cortex, and bilateral ventral striatum (VS). All neuroimaging analyses used a false discovery rate (FDR) multiple comparisons correction with a threshold of $p < .05$.

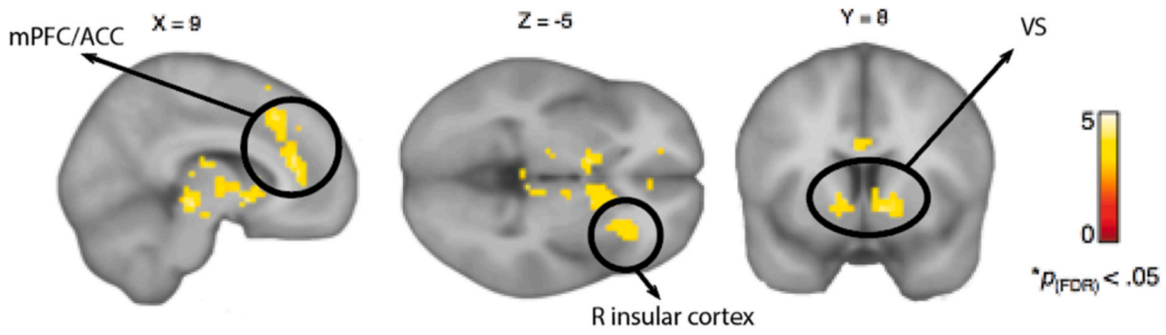

Fig. 3. *Linear Change in Neural Responses to Increasing Risk Across Waves.* Longitudinal whole-brain analysis showed a significant linear change in risk-related responses to increasing coefficient of variation (CV, i.e., risk) for chosen options across the three waves within the medial prefrontal cortex (mPFC, including the anterior cingulate cortex, ACC), right insular cortex, and bilateral ventral striatum. All neuroimaging analyses used a false discovery rate (FDR) multiple comparisons correction with a threshold of $p < .05$.

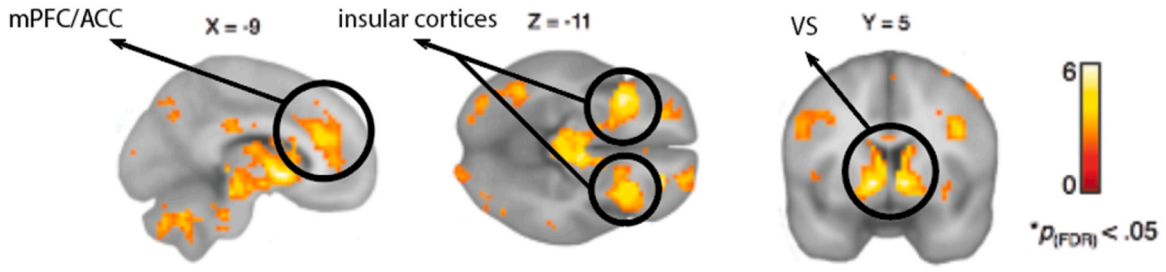

Fig. 4. Individual risk sensitivity estimates (averaged across three waves for each individual) correlated with mean risk-related BOLD responses, where decreased behavioral risk sensitivity (i.e., risk aversion) was related to responses associated with increasing risk (coefficient of variation; CV) in the medial prefontal cortex (mPFC, including the anterior cingulate cortex, ACC), bilateral insular cortex, and ventral striatum. All neuroimaging analyses used a false discovery rate (FDR) multiple comparisons correction with a threshold of $p < .05$.

representation of risk on average is consistent with brain areas implicated in encoding risk in adolescent (van Duijvenvoorde et al., 2015) and adult studies (Mohr, Biele, and Heekeren, 2010). This average risk-related activation was negatively correlated with behavioral estimates of risk sensitivity. Greater risk-averse behavior corresponded to increased recruitment of risk-related circuitry involving the medial prefrontal cortex, especially the anterior cingulate cortex, bilateral insular cortices, and ventral striatum.

Third, the development of risk-related processing in the adolescent brain changed linearly across time, with heightened neural responses for increased risk in the dorsal anterior cingulate cortex, right anterior insular cortex, and bilateral ventral striatum. The results presented here using a whole-brain longitudinal fMRI approach are consistent with our previous work using a region of interest approach that focused on the insular and dorsal anterior cingulate cortices only (Asscheman et al., 2020). Using a whole-brain longitudinal approach, we were able to identify additional brain regions (e.g., ventral striatum) that increased linearly in response to chosen riskier options during middle adolescence. Finally, health risk behaviors significantly increased during middle adolescence. Decreased risk-related brain activation in the right insular cortex at baseline (Wave 1) predicted steeper increases in health risk behavior change across three years. Adolescents with decreased neural sensitivity to processing risk information earlier in adolescence may represent a potential vulnerability for engagement in future risky behaviors. When adding behavioral risk sensitivity at baseline to the model, neural risk processing in the insular cortex at baseline became a non-significant predictor. The fact that behavioral risk sensitivity at baseline was a significant predictor of longitudinal increases in health risk behavior suggests that individual differences in risk processing in the brain may manifest in individual behavioral performance differences.

Prior research points to the importance of behavioral risk sensitivity

Table 3
Descriptive Statistics and Correlations between Study Variables within the Latent Growth Curve Models.

	M	*SD*	1	2	3	4	5	6	7	8	9
1. Health Risk Behaviors at W1	0.27	0.17									
2. Health Risk Behaviors at W2	0.29	0.21	.65 * * [.53,.74]								
3. Health Risk Behaviors at W3	0.34	0.23	.49 * * [.34,.61]	.65 * * [.53,.74]							
4. Right Insular Cortex	0.03	0.04	.06 [− .11,.23]	-.03 [− .20,.15]	-.12 [− .29,.06]						
5. Left Insular Cortex	0.03	0.04	-.00 [− .17,.16]	-.02 [− .19,.15]	-.10 [− .27,.08]	.87 * * [.82,.90]					
6. Left Ventral Striatum	0.02	0.03	-.03 [− .19,.14]	.05 [− .13,.22]	-.04 [− .21,.14]	.68 * * [.58,.76]	.65 * * [.54,.73]				
7. Right Ventral Striatum	0.02	0.03	-.04 [− .20,.13]	.02 [− .15,.19]	-.02 [− .19,.16]	.65 * * [.55,.74]	.60 * * [.49,.70]	.86 * * [.82,.90]			
8. Anterior Cingulate Cortex	0.05	0.06	-.06 [− .22,.11]	-.11 [− .28,.06]	-.10 [− .27,.08]	.80 * * [.73,.85]	.75 * * [.67,.81]	.66 * * [.56,.75]	.68 * * [.59,.76]		
9. Behavioral Risk Sensitivity at W1	-0.15	0.44	.03 [− .14,.20]	.22 * [.04,.37]	.19 * [.02,.35]	-.26 * * [− .40, − .10]	-.25 * * [− .40, − .09]	-.30 * * [− .44, − .15]	-.22 * * [− .37, − .06]	-.35 * * [− .48, − .19]	
10. Intelligence	43.74	5.39	-.16 [− .32,.01]	-.17 [− .34,.00]	-.13 [− .30,.04]	.04 [− .12,.20]	-.03 [− .20,.13]	.06 [− .11,.22]	-.01 [− .17,.16]	.06 [− .11,.22]	-.18 * [− .33, − .01]

Note. M and SD are used to represent mean and standard deviation, respectively. Values in square brackets indicate the 95% confidence interval for each correlation. * indicates $p < .05$. * * indicates $p < .01$, * ** $p < .001$.

and associated neural substrates in guiding individuals toward or away from risky behavior (van Duijvenvoorde et al., 2015; Kim-Spoon et al., 2016). Adolescents displayed greater risk-averse behavior in the lottery choice task over time, suggesting that they continue developing their behavioral preferences for risk. This is not surprising given the influx of novel experiences and ample opportunities to engage in risky behavior that often occur during the transition from early to middle adolescence. Adolescents became more stable in their risk preferences over time, which dovetails with a previous finding that adolescents exhibit more significant risk sensitivity variability than adults (van Duijvenvoorde et al., 2015). It may be that lower stability in behavioral risk sensitivity observed earlier in middle adolescence (compared to later in middle adolescence) indicates greater flexibility in one's propensity toward risk. Some evidence in line with this supposition was observed in the current study. A lower positive correlation was observed between Waves 1 and 2 than the positive correlation observed between Waves 2 and 3. An alternative explanation for greater variability or less stability in risk sensitivity earlier in adolescence may stem from adolescents learning how to use risk information. We would expect an increasing model fit to the data over time if this was the case. We observed successive increases in model fit over time assessed by the Akaike Information Criterion (AIC) such that model fits were better as adolescents increased in age ($AIC_{w1} = 9447.2$; $AIC_{w2} = 7679.5$; $AIC_{w3} = 7010.6$). In addition, greater risk seeking behavior in our experimental task at Wave 1 was associated with higher levels of adolescent health risk behaviors later on during middle adolescence (i.e., Waves 2 and 3), but not at baseline. The lack of a relationship at baseline between behavioral risk sensitivity and health risk behaviors is likely due to the low engagement in health risk behaviors for the group relative to later years. Taken altogether, our results point to early middle adolescence (i.e., around ages 13–14) as a critical time for shaping adolescents' behavioral preferences for risk that may lead to either risky or safe choices in the future.

There is a limited yet growing literature on how adolescents process risk information in the brain. The present study contributes to this work by examining how neural representations of risk change across critical years of middle adolescence. In line with other studies from other and our own research groups (Huettel, 2006; Mohr, Biele, and Heekeren, 2010; Paulus et al., 2003; Preuschoff et al., 2008; Lauharatanahirun et al., 2018; Li et al., 2019; Maciejewski et al., 2018; Asscheman et al., 2020), we found that adolescents represent risk in a network of regions previously implicated in risk processing including the medial prefrontal cortex, bilateral insular cortex, and bilateral ventral striatum. Much of the adolescent literature investigating change in neural correlates of risky decision-making assess change within a specific brain region rather than the whole brain. Using a longitudinal whole-brain analysis, we found that risk-related activations in the areas mentioned earlier increased linearly as adolescents become older. Heightened activation in these brain regions may reflect enhanced sensitivity to risk information and potentially indicates that this sensitivity may strengthen over time to guide adolescents away from potential adverse outcomes. The developing brain may become more efficient at calculating potential risks during decision-making over time. This maturation may explain the observed decreases in risky behavior in adulthood compared to adolescence (for review, see Defoe, Dubas, Figner, and van Aken, 2015;

Table 4
Latent Growth Curve Models for Development of Health Risk Behaviors from Wave 1 to Wave 3.

Unconditional Model										
	X^2		*df*		*p*	*CFI*		*TLI*		*RMSEA*
Model Fit	0.98		1		0.32	1.00		1.00		< .001
	Mean					Variance				
	B	*95% CI*	*SE*	*ß*	*p*	*B*	*95% CI*	*SE*	*ß*	*p*
Intercept	**0.26**	**[0.24, 0.27]**	**0.01**	**1.62**	**< .001**	**0.02**	**[0.01, 0.02]**	**0.005**	**1.00**	**< .001**
Slope	**0.03**	**[0.01, 0.04]**	**0.009**	**0.37**	**< .001**	**0.008**	**[.002, 0.01]**	**0.003**	**1.00**	**0.003**
Conditional Models for Right & Left Insula on Health Risk Behavior Change (Wave 1 – Wave 3)										
	X^2		*df*		*p*	*CFI*		*TLI*		*RMSEA*
Model Fit (R Insula)	4.52		4		0.34	0.99		0.98		0.03
Model Fit (L Insula)	4.83		4		0.30	0.99		0.98		0.03
Model Fit (R VS)	5.37		4		0.25	0.99		0.97		0.04
Model Fit (L VS)	6.42		4		0.16	0.98		0.95		0.06
Model Fit (ACC)	4.91		4		0.29	0.99		0.98		0.04
Influence of Right & Left Insula on Health Risk Behavior Change (Wave 1– Wave 3)										
			B	*95% CI*	*SE*		*ß*		*p*	
R Insula → Intercept			0.37	[− 0.35, 1.09]	0.37		0.08		0.32	
Intelligence → Intercept			**–0.005**	**[− .007,.003]**	**0.002**		**–0.17**		**0.04**	
R Insula → Slope			**–0.52**	**[− 0.97, − 0.06]**	**0.23**		**–0.22**		**0.02**	
L Insula → Intercept			0.07	[− 0.63, 0.77]	0.36		0.01		0.84	
L Insula → Slope			–0.32	[− 0.75, 0.11]	0.22		–0.14		0.16	
R VS → Intercept			–0.28	[. − 1.36,0.80]	0.55		–0.04		0.60	
R VS → Slope			–0.68	[− 0.76, 0.62]	0.35		0.02		0.84	
L VS → Intercept			–0.05	[− 1.11, 0.99]	0.53		–0.01		0.91	
L VS → Slope			–0.08	[− 0.75,0.58]	0.34		–0.02		0.79	
ACC → Intercept			–0.17	[− 0.67,0.33]	0.25		–0.06		0.48	
ACC → Slope			–0.12	[− 0.44,0.20]	0.16		–0.07		0.45	

Note. L = Left, R = Right, VS = Ventral Striatum and ACC = Anterior Cingulate Cortex. In the conditional models, intelligence and gender were included as covariates. Only significant covariate associations are reported. Significant associations are indicated in bold.

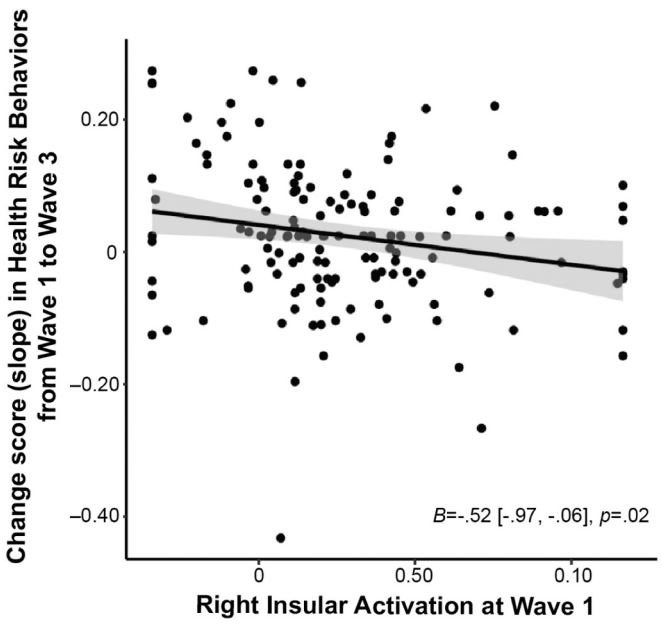

Fig. 5. *Relation between Wave 1 risk-related brain activation in the right insular cortex and the change in health risk behaviors from Wave 1 to Wave 3.*

Levin, Hart, Weller, and Harshman, 2007).

Much of the adolescent risky decision-making literature utilizing model-based approaches have yet to link inter-individual differences in neurobehavioral sensitivity to risk information to *prospective* real-world risk-taking. This is a meaningful connection if the goal is to use research to inform prevention and intervention efforts to decrease risk-taking behaviors. Here, we report for the first time that the encoding of risk information in the right insular cortex around the beginning of mid-adolescence (and not average insular cortex activation, see Supplementary Table 5) is a potential neural vulnerability for the future progression of health risk behavior. The importance of the right insular cortex in relation to health risk behaviors is further supported by our exploratory analyses showing that no other risk-related brain region (left and right ventral striatum and anterior cingulate cortex) was associated with changes in health risk behaviors during middle adolescence. The fact that we observed an association between right, not left, insular activation with health risk behaviors is not surprising as prior research in adults (Paulus et al., 2003) and adolescents (van Duijvenvoorde et al., 2015) have found similar lateralized results. Prior research suggests that the right and left insular cortex may be associated with lateralized autonomic nervous system functions (Montalbano and Shane Tubbs, 2018; Cohen et al., 2018; Craig, 2005). It is suggested that the left insular cortex is involved in activation of regulation and maintenance functions supported by the parasympathetic nervous system; whereas the right insular cortex is involved in the activation of the sympathetic nervous system which controls our responses to potential threats (Zhang et al., 1999). In light of this research, activation of the right insular cortex may signal the processing of aversive or threatening outcomes aiding in the anticipation and preparation for possible negative outcomes.

In sum, the present study's findings are important for three reasons: (i) provides a potential mechanistic explanation for why some adolescents make risky choices; (ii) identifies a possible neural vulnerability present early in middle adolescence for identifying at-risk adolescents susceptible to risky behavior with harmful health outcomes; and (iii) highlights the strength of a longitudinal design and model-based approach for understanding neurobehavioral processes of risky decision-making.

4.1. Limitations & future directions

Future studies should expand on the research presented here to examine time points before and after middle adolescence to discover when risk-related circuitry begins to develop and to capture the developmental trajectory of these processes. In addition, future work examining the trajectory of real-world health risk behaviors before and after middle adolescence alongside neural substrates of risky decision making would aid in a more comprehensive test of current neurodevelopmental

Table 5
Conditional Latent Growth Curve Model including Behavioral Risk Sensitivity at Wave 1 as a Covariate.

Conditional Models for Right & Left Insula on Health Risk Behavior Change (Wave 1 – Wave 3)						
	X^2	*df*	*p*	*CFI*	*TLI*	*RMSEA*
Model Fit (R Insula)	5.62	5	0.34	0.99	0.98	0.03
Influence of Right & Left Insula on Health Risk Behavior Change (Wave 1– Wave 3)						
	B	*SE*	*β*	*p*		
R Insula → Intercept	0.42	0.38	0.09	0.27		
R Insula → Slope	–0.40	0.23	–0.17	0.09		
Risk Sensitivity → Slope	**0.04**	**0.02**	**0.22**	**0.04**		

Note. In the conditional models, intelligence and gender were also included as covariates. There were no significant covariate effects on development of health risk behaviors. Significant associations are indicated in bold.

theories of adolescent risky behavior. Our study focused on a normative mid-adolescent sample so that the current findings may be more readily generalized to a relatively risk-averse mid-adolescent population. Future studies investigating risk-related decision-making processes in high-risk populations are needed. Furthermore, research has shown that risk taking behavior differs by domain (e.g., health, social, financial, etc.; Blais and Weber, 2006; Crone and van Duijvenvoorde, 2021). The findings of our study were specific to health risk behaviors and future research should examine whether risk-related brain areas are also prospectively related to risk taking in other domains beyond health.

While the focus of the current study was on the developmental trajectory of behavioral and neural risk sensitivity and its prospective associations to changes in health risk behaviors, future work examining risk and reward sensitivity interactions at the neural and behavioral levels would be fruitful in identifying precursors to potential risk or protective factors for developing psychopathology. For instance, it remains an open question as to whether greater levels of risk aversion provide potential protective effects against higher levels of reward sensitivity when engaging in risky decision-making. Furthermore, identifying whether there are gendered pathways to adolescent health risk behaviors via risk or reward processing systems remains an open area ripe for investigation. Being able to identify the longitudinal age-related changes in risk and reward sensitivity and how these changes might differ between genders has implications for guiding how to approach health risk behaviors in different genders.

Prior work has suggested that neural risk processing and cognitive control processes in the adolescent brain interact to predict adolescent health risk behaviors (Kim-Spoon et al., 2016, 2021; Maciejewski et al., 2018). Based on these studies, individual differences in cognitive control may help account for varying relations between neural risk sensitivity and adolescent risk-taking. That said, future work should examine the concomitant developmental processes of risk processing and cognitive control in the adolescent brain and the relation between these processes and risky adolescent behavior.

Although our results indicated that adolescents become more risk-averse over time, the specific mechanisms driving this pattern are unclear. Prominent theories in developmental psychology and developmental cognitive neuroscience have emphasized the importance of contextual factors such as home environment and peer influence and biological factors such as pubertal development in shaping the development of risk-taking behavior during adolescence into adulthood. For instance, adolescents have been shown to increase risk-taking when amongst peers (Chein et al., 2011). Regarding environmental influences, adolescents' insular risk-related processing was positively associated with parental monitoring in households with low, not high, chaos environments (Lauharatanahirun et al., 2018). The aforementioned result implies that adolescents' ability to develop sensitivity to potentially harmful stimuli may be affected by the environments in which they live. Future work should directly examine how these contextual factors (and their interactions) contribute to neurobehavioral risk processing and subsequent risk-taking behavior.

Moreover, risk-taking during adolescence is often described as maladaptive; however, increases in adolescent risk-taking are normative and can be adaptive for healthy development by promoting learning through exploration and approach toward novel experiences (Ellis et al., 2012). To better understand the mechanisms of maladaptive risky behavior, it is critical to study how risky decision-making processes develop within adaptive and maladaptive risk-taking domains.

In sum, our results suggest that "dual systems" neurodevelopmental theories may be more complex than previously described (Casey, 2015; Steinberg, 2008; Shulman et al., 2016). The overactive motivational system has been attributed primarily to reward-related processes reflecting the bulk of previous research focused on understanding reward sensitivity during adolescence (Barkley-Levenson and Galván, 2014; Braams, van Duijvenvoorde, Peper, and Crone, 2015; Galvan et al., 2006; Silverman, Jedd, and Luciana, 2015; van Leijenhorst et al., 2010). The present work illuminates that risk sensitivity (above and beyond reward sensitivity) is a promising neurobehavioral mechanism worthy of future research, given its prospective and concurrent relation to real-world risk-taking. Specifically, the fact that our results showed that behavioral reward sensitivity increased while behavioral risk sensitivity decreased during middle adolescence suggests that these two factors may be independent of one another. Conceptually, risk sensitivity and its neural substrates may be an important and separate mechanism that allows mid-adolescents to avoid potentially harmful outcomes. Given the extensive decision-making literature on neural risk processing (see Mohr et al., 2010), risk sensitivity may be akin to the avoidance system in the "triadic model" of motivated behavior that functions to process potential threats, negative affect, and aversive stimuli (Ernst et al., 2006) guiding adolescents away from negative outcomes. In the triadic model, the approach (i.e., ventral striatum) and avoidance systems (i.e., amygdala/insular cortices) are hypothesized to be hyperresponsive to both threats and rewards during adolescence with responsivity of these systems decreasing in adulthood. The cognitive control system is suggested to steadily increase in its development as age increases. Additional data regarding the development of risk sensitivity, reward sensitivity, and cognitive control during late adolescence would provide insights for refining current neurobehavioral developmental theories of adolescent risky behavior.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2023.101291.

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