Cortical and subcortical response to the anticipation of reward in high and average risk-taking adolescents.

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Author's Contribution

DK conceptualized the study, MD conceived and conducted the statistical analysis, wrote the draft of the manuscript and AJ provided support with the analyses. DK, EH, designed and executed the survey and the neuroimaging protocol. DK, EH, and AJ assisted MD with study conception and writing. All authors read and approved the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest

Abstract

Since the first neurodevelopmental model that sought to explain the influx of risk behaviors during adolescence was proposed (Ernst, Pine, & Hardin, 2006), there has been a series of iterations, criticisms and revisions. Despite limited ecological validity, the models have been used to propose studies and interpret results without establishing clear associations between the models and broad risk behaviors in adolescence. In an attempt to address recent criticisms and previous limitations, this study uses a targeted subsample of 104 adolescents (Age Mean = 18.9, SD = 1.3; Female 57%) composed of high (85th %ile and above) versus average (25th-50th %ile) risk takers from an ongoing longitudinal study assessing health risk behaviors (Wave 1 full sample = 2,017) to assess differential activation in regions of interest (ROI) proposed in prior neurodevelopmental models. The study employs two approaches to assess the links from neural activation differences to real world risk behaviors: *a priori* ROI evaluation; and a non-parametric whole brain analysis. Both are drawn from a big win vs neutral contrast in the Monetary Incentive Delay (MID) task. High and average risk profiles were characterized using both a Wave 1 (W1) measure of risk behavior and a multi-wave (MW) stable risk profile, based on 15 self-reported real-world risk behaviors. The ROI analysis revealed no differences between high and average risk profiles using either the W1 or MW (stable) classification of risk profile. In the whole brain analysis, W1 results showed significant differences between high and average riskers that were outside the ROIs proposed in prior literature, and no significant differences were found for the MW risk profile. These results indicate that the previous hypothesized models do not explain individual variation in risk profiles during anticipation of reward during MID task, and whole brain differences may depend on how risk-behavior profiles are defined.

69 *Keywords:* Risk Behaviors, Maturational Imbalance, Dual Systems, Triadic, Reward Sensitivity,
70 Adolescence
71

Introduction

Since adolescence was first characterized as a unique developmental stage by G. Stanley Hall in 1904 (Hall, 1904), the population has become of particular interest in policy and interventions aimed at reducing the high rates of mortality/morbidity that are exhibited during the developmental period (Dahl, Allen, Wilbrecht, & Suleiman, 2018). An overwhelming 70% of adolescent deaths in the United States are related to preventable causes, with a similar proportion of morbidity, from behaviors such as suicide, homicide, risky driving, risky sex and substance use (Casey, Getz, & Galvan, 2008; Kann, 2016). Although it has been recognized that risky behaviors contribute to the increased rates of morbidity and mortality in adolescence, programs that have been developed to reduce those risky behaviors have largely been ineffective (Steinberg, 2008). The incongruity of increased risky behaviors and improved reasoning skills in adolescence motivated a call for multi-disciplinary work across animal, neural, and behavioral domains to investigate key developmental changes that may contribute to these concerns (Dahl, 2004). This multi-disciplinary work has led to several neurodevelopmental models that have been critical in characterizing the developmental stage and effectively influencing public policy (Shulman et al., 2016; Steinberg, 2017). However, the studies have received substantial criticism due to the inconsistencies in findings and lack of convergence across key components of the models (Crone & Dahl, 2012; Meisel, Fosco, Hawk, & Colder, 2019; J. H. Pfeifer & Allen, 2012; Sherman, Steinberg, & Chein, 2018). This raises the question, do the prevailing models of neurodevelopment accurately characterize risk profiles?

Convergence in current neurodevelopment theories of adolescence have focused on developments in the socioemotional and cognitive control systems (Casey et al., 2008; Ernst, Pine, & Hardin, 2006; Luna & Wright, 2016; Steinberg, 2008). Socioemotional systems pertain

to reward sensitivity, such as sensation- and novelty-seeking. Changes in reward sensitivity encourage an organism to experiment with rewarding stimuli, such as social, sexual, substance and other risk behaviors. Sensation seeking is thought to be associated with basal dopamine (DA) levels, or tonic phase DA, that is driven by incentive motivation which enhances the engagement in a salient behavior (Ernst & Luciana, 2015). The proliferation of DA receptors in the midbrain following puberty are thought to give rise to increased sensitivity to salient stimuli and environments (Shulman et al., 2016). Meanwhile, the cognitive control systems are related to the proliferation of white matter (WM) and pruning of grey matter (GM; Mills et al., 2016; Tamnes et al., 2017), which may facilitate the specialization of cognitive processes and integration of neural networks (Marek, Hwang, Foran, Hallquist, & Luna, 2015) that can improve goal-oriented behaviors that encompass flexibility and forethought (Luna, Padmanabhan, & O’Hearn, 2010). Since early evidence demonstrated increases in WM and decreases in GM during adolescence (Giedd, 2004), a recent multi-sample longitudinal study replicated some of these earlier findings (Mills et al., 2016). As a result of increasing WM connections and decreasing overabundance of GM neurons, cognitive control systems are considered to improve and become more effective at goal-oriented decision-making and decreasing the impulsive nature related to risk behavior. A number of such dual process models (Steinberg, 2008) are described in more detail below.

Despite these similarities in process and function of socioemotional and cognitive systems across current neurodevelopmental models, there are key differences. The *Triadic model* (Ernst et al., 2006) focuses on the balance between approach, avoidant and regulatory systems. The approach system has positive valence, focused on rewarding stimuli, that drives an organism to engage in novel behaviors. Meanwhile, the avoidance system has negative valence, focused on

harm, which is involved in operant and conditioned behavior to help notify the organism of whether a stimulus should (or should not) be approached. The third component is the regulatory, or cognitive control system, which is critical in monitoring and adaptation, functioning as a conductor to facilitate behaviors by balancing information across multiple systems. The key systems in the Triadic model rely on different brain regions, specifically the approach system recruits both dorsolateral prefrontal cortex (dlPFC) and ventral striatum (VS); the avoidance system primarily involves the amygdala (central nucleus for operant behavior and lateral/basolateral for conditioning stimuli); and the regulatory system involves the medial PFC (mPFC), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC). All of these regions function in unison to exchange information and perform the goal-oriented behaviors.

As opposed to the balance across multiple systems in the Triadic model, the *Maturational Imbalance* (Casey et al., 2008), *Dual Systems* (Steinberg, 2008) and *Driven Dual Systems* (Luna & Wright, 2016) models emphasize the dominating or primary function of the cognitive control system to suppress inappropriate (or salient) thoughts and actions in favor of goal-oriented behaviors, reducing the effect of reward sensitivity. The Maturational Imbalance (Casey et al., 2008) model emphasizes that the inability to behave in a goal-oriented manner reflects immature development of the cognitive control system (ventral PFC [vPFC]) which reduces the influence of the OFC, involved in economic decisions, on reward sensitivity (Nucleus Accumbens [NAcc]). In contrast, the *Dual Systems* Model (Steinberg, 2008) contends that decisions are a clash between cognitive control (mPFC and OFC) and social-emotional (Amygdala and VS) regions. The early maturation of reward regions after puberty leads to increased reward seeking, especially in the context of peers, as a function of rising dopamine-rich receptors in the NAcc and decline in dopamine autoreceptors in the PFC, which is meant to function as a negative

feedback loop, reducing the PFC's ability to suppress inappropriate thoughts and actions. Similarly, the *Driven Dual Systems* model (Luna & Wright, 2016) contends that cognitive control is the key system in governing appropriate goal-oriented actions. However, this model posits that the cognitive control systems are largely developed by late childhood and early adolescence, and focus instead on the hyperactivation of the reward regions (VS) due to the proliferation of DA receptors that increase the appetitive/motivation systems, resulting in engagement in riskier behaviors.

Despite the several differences in the models, all four neurodevelopmental models emphasize the early sensitization of dopamine systems in reward regions following puberty, and the alteration of cognitive control and/or reward systems as a function of improved cognitive capacity, permitting adolescents to respond appropriately to salient stimuli and function in a goal-oriented manner. Critically, there is significant overlap between the brain regions discussed in the models: NAcc/VS, mPFC, dlPFC (Reward), Amygdala, vmPFC (Affective) and mPFC, ACC, OFC, vPFC (Regulatory). This offers an avenue of examining differences in patterns of neural activation and associations with risk behaviors.

Although there is substantial overlap in the brain regions in support of the models, there has been significant variability in neural findings and associated behaviors attributed to those regions, generating criticism and skepticism. A critical aspect in the neurodevelopment theories is the activation (or lack thereof) in support of cognitive and reward process. Some of the proposed regions in cognitive control systems have shown both activation and deactivation across age that have been difficult to reconcile (Crone & Dahl, 2012; J. H. Pfeifer & Allen, 2012). Moreover, despite overlaps in affective and social processes, adolescent research has predominately focused on monetary value in VS (Crone & Dahl, 2012; Ernst, 2014). While some

of these neural signatures of VS and PFC activation may be related to atypical development, they may not be representative of typically developing youth (Bjork & Pardini, 2015). As a result, the models suggest predispositions in neurodevelopment in adolescence that biases them towards risky behaviors (Pfeifer & Allen, 2012). Moreover, the peaks in reward processing in the dual system models precede the peaks of unintentional injury by several years (Bjork & Pardini, 2015).

Although the models are frequently used to interpret and predict associations, the original theories were predominately based on ‘*reasonable speculation*’ (Steinberg, 2008, pp. 81) and encouraged for use as a ‘*schematic that should lead to formulation of more comprehensive models*’ (Ernst et al., 2006, pp. 300). One key domain of the model is the alteration of DA receptors in reward sensitive VS. While animal models have shown that there is a rapid rise of DA in NAcc/VS (Ernst & Luciana, 2015), there are also important differences and changes in DA of the dorsal striatum (DS) and mPFC (Romer, Reyna, & Satterthwaite, 2017). The extracellular concentrations of DA are higher in the DS than the core or shell of VS (Marinelli, 2007). This may be important with respect to action-selection, as primate work has demonstrated value encoding in both DS and VS (Haber & Behrens, 2014; Padoa-Schioppa & Conen, 2017). Further, changes in DA in mPFC may be notable as they coincide with the peaks in sensation seeking (Romer, 2010; Steinberg et al., 2018), behavioral approach systems (Doremus-Fitzwater & Spear, 2016), and rise in unintentional injury in late adolescence (Centers for Disease Control and Prevention, 2019). Romer et al. (2017) noted that the changes in sensation seeking may be associated with PFC activation, which may be a function of learned valuation.

While there has been speculation about neural associations among psychological, neurobiological, and risk behavior development, convergent and ecological validity has been

scant. One presumed association is in the neurobiological (reward sensitivity) and psychological (sensation seeking) pathways to risk taking behaviors (Shulman et al., 2016). A large proportion of studies investigating risk behaviors and neural change have relied on cognitive measures in laboratory settings as ‘scanner-compatible proxies for measuring real-world behaviors’ (Telzer, Fuligni, Lieberman, Miernicki, & Galván, 2015, pp. 391) or ‘ecologically valid measure of real-life risk taking’ (Qu, Fuligni, Galvan, & Telzer, 2015, pp. 11309). However, the use of proxy variables, such as cognitive task performance to identify risk behavior profiles as a dependent variable, may be problematic owing to their questionable construct validity (Demidenko, Huntley, Martz, & Keating, 2019). In addition, mixed results regarding adolescent neurodevelopment may reflect initial differences in the selection of parameters and locations in neuroimaging analyses rather than conflicting results. Specification and justification of these choices is thus paramount for efforts to accumulate evidence on these questions (Demidenko et al., 2019). Key differences in parameter decisions may invoke differing results, especially when the parameters are infrequently studied in the context of risk.

Recent reviews that have examined neural predictors of risk behaviors in adolescents report substantial variability across studies and lack of support for the neurodevelopmental models. More specifically, multiple reviews reported that comparison groups have had high variability in categorizing children, adolescents and adults (Crone & Dahl, 2012; Galván, 2010). Further, tasks have often utilized different analytic strategies, baseline conditions, and magnitudes (or probabilities) of reward. Sherman et al. (2018) found in their review that risk taking indexed by different neural correlates is measured in different ways across studies, categorized for example by lab-based measures of risk in task (which may be largely ineffective), generalized sensation-seeking, or perceptions of risks. In addition, 70% of the

studies they reviewed were severely underpowered ($N < 50$) and oftentimes researchers solely used region of interest (ROI) approaches, focusing attention where findings were expected, overlooking alternative key regions posited by alternative models. The latter may be problematic, as it is often difficult to determine how close two coordinates from different studies have to be to be considered as a replication (Hong, Yoo, Han, Wager, & Woo, 2019).

To overcome previous limitations of sample size, broad age ranges, inefficient proxies of real-world risk, and variable analyses options, this study evaluates neural activation profiles in adolescents that are associated with self-reported real-world risk behaviors. A large and diverse population of typically developing high school adolescents (10th and 12th graders) were recruited. In light of the evolutionary normative processes often exhibited as ‘risk taking’ in adolescence and the role of experiences providing adaptive challenges (Casey, 2015), adolescents provided self-reports on risk behaviors in multiple categories. A subsample of adolescents was classified into high (85th percentile and above) and average risk groups (25th – 50th percentile) based on these self-reports (from a confirmatory factor analysis across all risk behavior categories), and were recruited for a neuroimaging protocol to evaluate differences in neural activity associated with the level of risk behavior, utilizing both whole brain analyses and a list of key *a priori* brain regions (ROIs) from an empirical consensus based on the research literature. In a subsequent comparison, high- and average-risk groups neural activation profiles were assessed based on the longitudinal stability of their risk profiles over time. A modified Monetary Incentive Delay (MID) task that is comparable to the task used in the IMAGEN project (Cao et al., 2019) and identical to the task used in the Adolescent Cognitive Brain Development (ABCD) study (Casey et al., 2018) was administered in a functional magnetic resonance imaging (fMRI) session. Using both whole brain and consensus ROI approaches, this is the first study to our knowledge to

assess whether the neuroimaging results show the predicted differences between high versus average risk-taking adolescents. Based on theoretical models and available neuroimaging studies, it was hypothesized that the high-risk group would exhibit increased VS, amygdala or OFC and decreased dlPFC activation.

Methods

Participants

Participants in this neuroimaging study are from a subsample of the Adolescent Health Risk Behavior (AHRB) study, which is designed to characterize behavioral, cognitive, psychosocial and neural correlates of adolescents' risk behavior trajectories. AHRB consists of a nonprobability sample of 2,017 (Age Mean = 16.8, SD = 1.1; Female 56%) 10th and 12th grade students recruited from nine public school districts across eight Southeastern Michigan counties, using a quota sampling design to maximize socioeconomic, racial and ethnic diversity. Phase I of the study is described elsewhere. Study procedures were approved by an Institutional Review Board. From Phase I of the study, a subsample of 115 adolescents were recruited to participate in Phase 2, the neuroimaging phase of the study (Days after first Wave: M = 30.9 months SD = 5.0 months). Participants that were identified as belonging in high versus average risk behavior categories, based on a factor-analyzed Behavioral Misadventure Scale (BMS) that incorporated all risk behavior categories, were invited to participate in the neuroimaging phase. Of the 115 adolescents that participated, 108 completed the magnetic resonance imaging (MRI) portion of the visit. Seven participants (N = 6, average risk; N = 1, high risk) were ineligible or unable to participate in the MRI due to not meeting MRI safety eligibility e.g. claustrophobia (N = 3) or no formally documented medical clearance to rule out potential metal in body (N = 4). Of the 108 participants that completed the MRI, four participants were excluded from the analyses due to:

artifacts in the images that were not recoverable (N = 2, average risk; N = 1, high risk), and another due to stopping to respond during the task (N = 1, average risk). The final fMRI subsample (N = 104; Age Mean = 18.9, SD = 1.3; Female 57%) was included in the subsequent analyses and did not differ from the full sample in age, gender, or time from the original survey.

Risk Group: Behavioral Misadventure

To summarize overall engagement in risk behavior and give adequate weighting for low frequency but high impact risk behaviors that could be used in identifying risk profiles, the entire sample was randomized into two halves to conduct a principal component analysis (PCA) with the first half and a confirmatory factor analysis (CFA) with the remaining half. Three components were derived from the PCA (Promax rotation) accounting for 53% of the variance. A CFA with maximum likelihood estimation was utilized to evaluate the fit of a second order factor structure consisting of a behavioral misadventure factor comprised of the three components identified from the initial PCA. The fit indices indicated a satisfactory fit RMSEA = .06, RMSEA 90% CI = .05 - .07, SRMS = .04, CFI = .92. A behavioral misadventure factor score (BMS) was saved for the entire sample and used in subsequent analyses (Cronbach α = .78). In addition, several specific health risk indicators were investigated individually, selected because of their frequency of use in prior research: substance use; risky sex; and risky driving. Based on this latent factor score, a high-risk group was classified based on an 85th percentile cutoff, and an average risk group based on falling within the 25th to 50th percentile. This produced distinct groups that were non-overlapping (Figure S1).

fMRI Task

To evaluate the neural activation of reward processing, the Monetary Incentive Delay (MID) Task was used to model the neural signatures of the anticipation of monetary reward

(Knutson, Westdorp, Kaiser, & Hommer, 2000). The MID is a well-established task for assessing reward processing and is currently being employed across 21-sites in the national Adolescent Brain Cognitive Development (ABCD) study to measure the development of adolescent reward processing (Casey et al., 2018). Identical to the task described in Casey et al. (2018), the task in this study consists of three phases: anticipation, probe and outcome (that is, feedback). Each trial starts with a cue type (Win \$0.20, Win \$5, Lose \$5, Lose \$0.50, or No Money At Stake). Each cue lasts for 2000ms and is followed by a jittered fixation cross (1500-4000ms). Following the jittered fixation cross, the target probe cue (187-500ms) appears that requires participants to respond in order to win or not lose money. If participants are too fast (or too slow), that trial is marked as incorrect. Following the probe phase, the outcome (or feedback) phase (2000ms minus the target duration) indicates the outcome of that trial (for example, 'You Win \$5!', 'You Keep \$0.20', 'You Lose \$5' or 'No Money At Stake!'). There are twelve trial orders of the task, consisting of 50 contiguous trials and 10 trial types per run (5:42 minutes long). Participants complete two runs of the MID task during the scan (Total: 100 contiguous trials and 20 trial types). The task is individualized with an initial mean response time (MRT) that is used from the practice run performed outside of the scanner minutes before the scan. Using the average reaction time (RT) plus two standard deviations on correct trials, the MID task individualizes the difficulty to reach around 60% accuracy rate by adjusting the difficulty (that is, probe duration). See Figure S2 in Supplementary Materials for a schematic of the task.

Prior to the scan, participants were informed of all cue-related outcomes and completed a practice trial of the MID task. Participants were explicitly told that their performance on the task during the scan (for example, \$5 Win Cue is was associated with an opportunity to win \$5 and a \$5 Lose cue was associated with an opportunity to not lose \$5) will be associated with the

302 compensation they can get for their cumulative earnings during the MID (Maximum \$30).

303 Stimuli were presented via the IFIS system (MRI Devices, Inc., Milwaukee, WI), an integrated

304 stimulus display and experimental control package, also capable of recording button presses.

305 Lenses were available with the IFIS system to correct subject vision, as needed.

306 *fMRI Data Acquisition*

307 Subjects spent approximately 1 hour in the bore of the magnet, for MRI data acquisitions.

308 Data were acquired using a GE Discovery MR750 3.0 Tesla scanner with a standard adult-sized

309 coil (Milwaukee, WI). A full-brain high-resolution T1 SPGR PROMO scan was acquired that is

310 used in preprocessing (TR = 7000ms, TE = 2900ms, flip angle = 8°, FOV = 25.6 cm, slice

311 thickness = 1 mm, 208 sagittal slices; matrix = 256 x 256). Before the MID task, a fieldmap was

312 acquired using spin-echo EPI (TR = 7400ms, TE = 80 ms, FOV = 21.6 cm, 90x90 matrix) with

313 opposite phase encoding polarity (A→P, P→A). Two functional T2*-weighted BOLD MID runs

314 were acquired in the axial plane following structural and a faces task using a multiband EPI

315 sequence (MB factor=6) of 60 contiguous axial 2.4 mm slices (TR = 800ms, TE = 30 ms, flip

316 angle = 52°, FOV = 21.6 cm, 90x90 matrix, volumes = 407).

317 *fMRI Data Analyses*

318 FMRI data were reconstructed and realigned using SPM12, physiological noise was

319 removed using RETROICOR, and a fieldmap correction was applied in SPM12 to each T2* run

320 to recover inhomogeneity of signal in the B0 field. Preprocessing steps were completed using

321 FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) FEAT (FMRI Expert Analysis Tool)

322 Version 6.00. Our preprocessing steps included: registration to high resolution structural and

323 standard space MNI 152 image using FLIRT (Jenkinson & Smith, 2001; Jenkinson, Bannister,

324 Brady, & Smith, 2002), motion correction using MCFLIRT (Jenkinson et al., 2002), non-brain

removal using BET (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 5mm, grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor and highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma=50.0s$).

First-level analyses were performed by using FEAT. Time-series statistical analysis was carried out using FILM with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Similar to other studies (Cao et al., 2019; Hagler et al., 2019; Lamm et al., 2014), both Anticipation and Feedback events were modeled (15 explanatory variables), in addition to six motion parameters (translations and rotations in x,y,z directions) and the derivatives of the motion parameters. Anticipation events included: Big Win, Small Win, Neutral and Small Lose condition cues. Feedback included both hit and miss events for: Big Win, Small Win, Neutral, Small Lose, Big Lose. To control for the temporal effect of motion of the BOLD signal, we used an additional confound list to censor frame displacement (FD) volumes that exceeded $FD > .9$, this matrix was derived using *fsl_motion_outliers*. To average across the two runs, a second-level model was defined for each participant using fixed effect analysis in FEAT.

Whole Brain: Group-level analyses were performed using non-parametric permutation tests to create null non-parametric distributions and control type 1 error rates (Eklund, Nichols, & Knutsson, 2016), with cluster correction performed using Threshold-Free Cluster Enhancement (TFCE) in order to accurately differentiate both focal and broad level activation that may be lost using standard parametric models (Smith & Nichols, 2009; Winkler, Ridgway, Webster, Smith, & Nichols, 2014). As described in Pfeifer et al. (2019), nonparametric models reduce assumptions about spatial distributions of noise within fMRI and reduce false positive rates. A design matrix was used differentiating group (High vs Average risk), with a covariate of

age that was demeaned and entered into the model. To perform the analysis, FSL's *randomise* command (5000 permutations) was used with zstat files produced from Feat Second Level's for the contrast Big Win > Neutral. A cluster-level threshold of FWE-corrected $p < 0.05$ was used to identify significant values in the statistical maps for a mask (Supplementary Figure S4).

Region of Interest: A priori regions of interest (ROI) from Neurosynth (www.neurosynth.org) were used to evaluate differences of mean signal intensity in high vs average risk groups. These regions were selected based on overlap in original descriptions of the dual systems models and from 20 studies (totaling 70 coordinates, with overlap; see Supplementary Table S1 and Figure S3a) described in two reviews of adolescent neurodevelopment and risk behavior (reviewed in Galván, 2010; Sherman et al., 2018). Due to multiple peaks in the vmPFC region defined on Neurosynth, the NIFTI file was downloaded and thresholded in fsleyes in conjunction with coordinates from the 20 study meta-analysis that referred to the vmPFC. A central (ventral) peak from the Neurosynth ROI (see Figure S3b) was selected that overlapped with the coordinates from the ROI meta-analysis that was consistent with function in secondary rewards (Haber & Behrens, 2014). A list of Neurosynth MNI coordinates (Supplementary Table S2), were converted into voxel space. The central voxel coordinates for ROI's were used with *fslmaths* to create 10mm spheres. For each ROI, the voxels from each contrast mask (using z-statistics produced by Feat Second Level) were averaged to create a mean signal intensity value that was extracted using *fslmeants* and used in analyses in R version 3.6.1 (R Core Team, 2019). To control the type I error rate and consider relationships among ROI's that may differentiate risk and age profiles, a Multivariate analysis of variance (MANOVA) was performed. Subsequently, to examine the unique association between risk profile and mean signal intensity of each ROI, fourteen multiple regression models are

performed, controlling for age. To control for multiple comparisons (14 multiple regression models), rather than using a highly conservative Bonferroni correction, a less conservative False Discovery Rate (FDR) was used, and adjusted p-values are reported where significant differences arise (Benjamini & Yekutieli, 2001; Noble, 2009). The FDR rate was calculated by including an array of p-values from the models of interest into the `p.adjust()` function in R (“BH” method), which returns an array of adjusted values. FMRI Scripts and files used in these ROI and permutation analyses (with associated output files) are made available on github (TBD).

Post-hoc analyses

To evaluate the effects of stable risk profiles, a combination of waves administering self-report measures of risky behaviors were used to define ‘stable high’ (that is, 85th percentile or higher on two waves of survey response) and ‘stable average’ (25th-75th percentile on two waves) risk profiles. These profiles were used to re-examine the ROI and whole brain analyses to determine whether there are significant differences between the persistently high versus average/low risk behavior profiles used to predict neural activation. This method may evoke differing neural properties that may capture robust individual differences in problematic behaviors as opposed to a single snapshot of risk engagement.

Results

Descriptive and Behavioral: High risk (N = 41) and average risk (N = 63) groups varied on a couple demographic variables. There were no significant differences in time before wave 1 and scan 1 ($p > .05$; Figure S5) As expected, those in the high risk group were significantly older ($p < .01$, $d = .52$; $M = 19.3$, $SD = 1.4$) than those in the average risk group ($M = 18.6$, $SD = 1.3$). Conversely, those in the high risk group had significantly lower IQ ($p < .05$, $d = .41$) than the average risk group ($M = 101.1$, $SD = 11.7$ versus $M = 106.1$ $SD = 12.2$). There were no

significant differences on parental level of education between high ($M = 4.1$, $SD = 1.2$) and average risk ($M = 4.4$, $SD = 1.1$) groups (see Table 1).

With respect to behavioral performance on the MID, there were no significant group differences between overall performance (accuracy and response times) in the high and average risk groups ($p > .05$) during MID trials, nor for big win or neutral trials (Table 1; Figure S6). Notably, response times were only collected by E-Prime for accurate trials, so we only report on the variation in regards to response times with respect to hit and not miss trials (Figure S7).

Region of Interest (ROI) Analyses:

First, to examine the association between neural correlates to the contrast of anticipation of big reward vs neutral and adolescent risk behaviors, we used *a priori* ROI's to examine recent theoretical models. To analyze the unique variance among the 14 ROI's, the MANOVA revealed no significant difference between risk profiles (average vs high), Wilk's lambda = .83 $F(14, 87) = 1.26$, $p = .25$, nor an interactive effect of risk group (high vs avg/low) and age, Wilk's lambda = .93 $F(14, 87) = 0.93$, $p = .95$. This indicated that there were no unique relationships among the fourteen ROI's that are associated with age or self-reported risk. In the multiple regression models examining the association between risk profile (high vs average risk) and activation to the anticipation of big reward in 14 ROI's, controlling for age, there were no significant associations when correcting for multiple comparisons (Supplementary Table S3 for corrected and uncorrected values). When *uncorrected*, there was a significant association between Left Dorsolateral Prefrontal Cortex ($B = -.62$, $p < .05$) and Right Posterior Parietal Cortex ($B = -.63$, $p < .05$), whereby higher activation is associated with a lower risk profile. However, each of these uncorrected associations explained only 5% of the variance.

Whole Brain Analyses

Second, to examine whether average risk (N = 63) and high risk (N = 41) groups differed in neural activation during the contrast of anticipation of big reward vs neutral conditions that were not influenced by *a priori* ROI selection, we conducted a nonparametric TFCE whole brain analysis (controlling for age). Across both groups, the MID task evoked robust activation of the ventral striatum (Figure S8). Contrary to the hypothesized neurodevelopmental models, however, and reflecting inconsistencies in recent literature, the whole brain analysis revealed no significant differences in regions selected for the aforementioned ROI analysis. Moreover, the high risk group (N = 41) did not exhibit greater activation in any voxels/clusters as compared to the average-risk group (N = 63). However, consistent with recent evidence (Sherman, Steinberg, & Chein, 2018), in a direct contrast between groups, the average risk group exhibited several significant clusters in the whole brain analysis as compared to the high-risk group. Specifically, the average-risk group had greater activation ($p < .05$) in the dorsal striatal, precuneus, posterior parietal, primary visual, primary cortex, and cerebellar regions (See Table 2; Figure 1). Although not predicted *a priori*, this pattern suggests greater activation among average risk takers in action-oriented regions.

Post-hoc analyses

Descriptive: Out of the original sample of 104 high and average risk-taking adolescents based on a BMS score derived from Wave 1, two waves of data were used to define stable high and stable average risk profiles. As expected, there was a significant difference in the number of adolescents moving to high vs average risk group ($X(1) = 8.22, p < .01, \Phi = .29$), whereby 23 adolescents (Mean Age = 18.4, SD = 1.1) moved from the average to high risk group, and five (Mean Age = 19.0, SD = 1.4) adolescents moved from the high to average risk group when using multi-wave information to compose a stable risk profile. These transitioning groups did not

significantly differ from the remaining sample on age, sex, parental education or IQ ($p > .05$). After excluding adolescents that transitioned to different risk profiles ($N = 27$) and those that did not complete a questionnaire in a subsequent wave ($N = 6$), this reduced the subsample to 71 adolescents, 37 stable average-risk ($M \text{ Age} = 18.6, SD = 1.3$) and 34 stable high-risk ($\text{Mean Age} = 19.4, SD = 1.3$) adolescents. Analyses between the stable high and average-risk groups afforded an opportunity for a more stringent test of this individual difference contrast.

Region of Interest Analysis: The post-hoc analyses evaluating ROI differences in stable high vs stable average risk takers demonstrated comparable results to the wave 1 risk profile. Specifically, the analysis of unique variance among the 14 ROI's, the MANOVA revealed no significant association between risk profile (average vs high), Wilk's lambda = .70 $F(14, 54) = 1.66, p = .09$, and no interactive effect of group of risk (high vs avg/low) and age, Wilk's lambda = .86 $F(14, 54) = 0.61, p = .84$. Similar to Wave 1 risk profiles, stability of profiles over time did not reveal a unique relationship among the fourteen ROI's. Moreover, the fourteen multiple regression models revealed comparable results to the wave 1 risk groups. In the multiple regression models, when corrected for multiple comparisons, there were no significant associations (Supplementary Table S3 for corrected and uncorrected values). When *uncorrected*, there was a significant association between Right Dorsolateral Prefrontal Cortex ($B = -.79, p < .05$) and Right Posterior Parietal Cortex ($B = -.72, p < .05$), whereby higher activation is associated with a lower risk profile. Both of these models explained only 9% of variance in the models.

Whole Brain Analyses: The post-hoc analysis evaluating differences of whole brain activation to the anticipation of big reward in stable high vs stable average risk takers demonstrated different results from that of Wave 1 sample defining risk profiles. Specifically,

the nonparametric TFCE analysis revealed no-significant clusters that surpassed the $\alpha < .05$. At a lower threshold of $\alpha < .08$, in a direct contrast between groups, revealed clusters that were significant in the initial analysis (See Table 2; Figure 2), specifically greater activation in anterior cingulate ($p = .07$), Left Precuneus ($p = .07$), Left Caudate ($p = .07$) in average as compared high risk takers. Likewise, at a lower threshold ($p < .08$), average risk takers demonstrated greater activation in Right dlPFC ($p = .05$), Right Premotor ($p = .07$), Anterior Cingulate ($p = .07$), Right Precuneus ($p = .07$), Right SMA ($p = .08$) and Right Precentral Gyrus ($p = .08$). These results suggest some convergence, while also some variability between single vs multiple assessment of risk profiles in whole brain activation that necessitates increase power. Notably, using the Euclidean distance between peak coordinates

$$\sqrt{(x_{whole\ brain} - x_{ROI})^2 + (y_{whole\ brain} - y_{ROI})^2 + (z_{whole\ brain} - z_{ROI})^2}$$

used in Hong et al. (2019, pp. 387), comparing the peak location of DLPFC in the whole brain results to that of the *a priori* DLPFC coordinate, there was a 64.5mm distance between peaks, suggesting strong difference in the location of peak activation. Further, similar to the subsample (N = 71) and full sample (N = 104), the right dlPFC was present only at a lower threshold, $p = .05$ and $p = .06$, respectively.

Discussion

Over the course of the last 15-years, several neurodevelopmental models have been proposed as a way to explain the rise in risky behaviors during mid-to-late adolescence. Despite a strong commitment to exploring the neural differences in cognitive control and reward processing across a broad age-range, inconsistencies in definitions of risk and parameter selection have led to mixed interpretations (Crone & Dahl, 2012). Furthermore, proxies of risk behaviors and *a priori* region of interest (ROI) analyses have contributed to heterogeneous

results that have not replicated theoretical models (Sherman et al., 2018). To our knowledge, this study is the first to use several ecological measures to derive high and average risk groups, as well as longitudinally stable high and stable average risk-taking profiles in adolescents to explore prospective neurodevelopmental differences using both *a priori* ROI and whole brain analyses. The variability in results and lack of evidence for neurodevelopmental heuristics in prior studies may be related to sample sizes, independent variable and parameter selection, and assuming homogeneity in adolescents.

Using predefined ROI's based on neurodevelopmental models and prior literature, there was little evidence for systematic variability between high vs average risk-taking adolescents. Although frequently researched regions or the 'hot spots' of reward processing (Woo, Chang, Lindquist, & Wager, 2017), such as the ventral striatum, produced robust activation in statistical maps during the anticipation of a big monetary reward compared to a neutral cue, this activation did not differentiate risk profiles in adolescents. Although two regions involved in higher order cognitive processing, the dorsolateral (dlPFC) and posterior parietal cortices (PPC), significantly differing across high and average risk groups, their effects were small in the two ROI analyses and, more important, they did not survive multiple comparison corrections. In some ways, this latter finding supports the notion evoked by Sherman et al. (2018), that 'outcomes tend to emerge where one goes looking' (pp. 32).

To avoid constraining interpretations to *a priori* ROI's and behavioral properties of the task, a nonparametric analysis on the whole brain was conducted that revealed significant clusters that varied across the defining criteria for high and average risk profiles. In the initial comparison that used self-report risk behavior measures from the first wave, the comparison of high risk and average risk takers revealed increased activation across a broad range of regions.

These included the dorsal striatal, primary visual, primary motor, precuneus, posterior cingulate and cerebellar regions. This activation revealed an action-oriented representation. However, when using multiple waves to identify stable high and stable average risk profiles, the activation differed from the initial whole brain analysis. Specifically, neither of the clusters of activation from the initial analysis were represented in the stable high and stable average risk analysis at an $\alpha < .05$. However, when the $\alpha < .05$ was lowered, the caudate, cingulate cortex and precuneus were both represented, in addition to the right dorsolateral prefrontal cortex, SMA and the precentral gyrus. Based on speculation, these latter findings may suggest a lack of power, but taken together, the findings indicate differences in independent variable and parameter selection as well as heterogeneity across subjects that impacts results. Further, seeing as the stable high and stable average comparison produced activation that trended towards significance in the DLPFC, this area varied from our *a priori* ROI selection, providing evidence of how researcher degrees of freedom and flexibility in spatial selection can impact results (Hong et al., 2019).

Recent inconsistencies in findings can be attributed to multiple sources, one of which is sample sizes that may contribute to ‘voodoo’ correlations (Vul, Harris, Winkielman, & Pashler, 2009). It is apparent from a recent review that neuroimaging studies suffer from small samples, whereby the average sample size in adolescent risk behavior literature is less than 50 participants (Galván, 2010; Sherman et al., 2018). Reviews of early fMRI research demonstrated that often a strategy was to compute separate correlations of voxels/clusters with behavior that exceeded a threshold in a group level map, these correlations with behavior on occasion even exceeded intraclass correlations of regions of interest (Vul et al., 2009). Some of these correlations are attributable to extremely small samples, systematically inflating correlation between neural activation and behavior (Yarkoni, 2009). This can be represented by pulling out the statistics for

nine of the studies in the Table 2 in Sherman et al. (2018, pp. 35-35), which demonstrates that the magnitude of the correlation was related to the sample size ($r = .64$), with the smallest ($r = .12$) and largest ($r = .77$) correlation in a sample of 324 and 7, respectively. Reiterating the rate of biases that result from small samples (Yarkoni, 2009), likely contributing to the >50% rate of false positives in neuroimaging studies (Szucs & Ioannidis, 2017).

In addition to small samples, parameter selection is often overlooked. In the 23 studies identified in Table 1 in Sherman et al. (2018), the most commonly used task was the MID, highlighted in four of the 23 studies, whereas the next most common task was only used twice. These differences make it difficult to discern the neural correlates with behavior. Animal models have demonstrated that learning what to and not to approach is variable, while some circuits are related to prediction error, others may be related to goal-oriented models (Eshel & Steinberg, 2018). For example, the MID, wheel of fortune or balloon analogue risk task may relate to distinct circuits that exhibit a role important in learning the action and event values through trial and error, whereas affective and peer paradigms may relate to efferent working models that make decisions regarding future events that may impact goal-directed choice. In the latter decision-based model, values are estimated with each action using inferences based on costs, benefits and some forms of neural signals ability to generalize to new situations (Rangel & Hare, 2010; Schultz, 2015).

These distinctions may be critical as there are heterogeneities in animal behaviors, whereby some rely on a trial-and-error and others on goal-directed choice (Eshel & Steinberg, 2018). With respect to neural properties, such intricacies may impact the region of activation. Although the VS/NAcc dominant the core principals of the neurodevelopmental models of risk/reward processing, work in animal and human models have demonstrated that neural

processing may depend on various aspects, some of which include: type of learning (or encoding paradigm); whether the processing relates to afferent or efferent systems; whether a reward is contingent on action and if a reward is primary or secondary (Haber & Behrens, 2014; Padoa-Schioppa & Conen, 2017; Szczepanski & Knight, 2014). These distinctions are critical in assessing whether results do (or do not) converge across studies and have a similar predictive utility.

Outside of the domain of neural estimates, there is substantial heterogeneity in the behavioral definition of risky behaviors. Research on normative samples often utilizes variables that may not be ecologically valid proxies of really world risk behavior. While some use psychological characteristics such as sensation seeking (Bjork, Knutson, & Hommer, 2008), general measures of risky behaviors (Op de Macks et al., 2016; Saxbe, Piero, Immordino-Yang, Kaplan, & Margolin, 2015), substance use (Chung et al., 2015; Bjork et al., 2011) or likelihood of engaging in future risk (Galvan et al., 2007), several studies associate neural activation as a function of risk as measures by the task, such as driving (Cascio et al., 2015), probability or gambling tasks (Eshel, Nelson, Blair, Pine, & Ernst, 2007; Op de Macks et al., 2016; Qu et al., 2015; Telzer et al., 2015). These proxy-based measures of risky behavior may be inappropriate as laboratory tasks may require larger samples to capture small effects (Sherman et al., 2018) that have limited evidence for age-related differences de(Defoe, Dubas, Figner, & van Aken, 2015), and often serve as poor predictors of real-world risk behaviors in normative adolescent populations (Demidenko et al., 2019). Furthermore, if neurodevelopmental models are to use indicators of sensation seeking or reward sensitivity, it is important to recognize that these indicators vary in their association with different risky behaviors (Demidenko et al., 2019).

Finally, there is increasing evidence that adolescent behavior is heterogeneous and that this behavior should be modeled as such (Bjork & Pardini, 2015; Sherman et al., 2018). With respect to the dynamic system of the brain, the assumption that individuals are homogenous is often violated (Beltz, Wright, Sprague, & Molenaar, 2016), and thus it is important to identify unique and similar patterns in the individuals that may be used systematically to more effectively explain behavioral change (Beltz & Gates, 2017). This alternative technique may be more appropriate in identifying networks that may offer some stability of measurement within and between participants, as opposed to the mean-level task effects that often have poor test-retest reliability (Elliott et al., 2019). For example, although two substance users on paper may look similar, the neural activation may vary as a function of attention, motivation, pleasure that are based on differential reward signals (Schultz, 2015), resulting in mean-activation during events of a task that will vary but may reflect similar patterns in their neural dynamics that are missed in a ‘pooling’ of activation. Alternatively, since the location of activation in a particular region may vary between samples (or individuals), such as the dorsal anterior cingulate may vary between samples (Hong et al., 2019), response-patterns may be an alternative method to model differences in location and timing of the signal (Haxby et al., 2011). Moving forward, a measure that accounts for the brain being a dynamic and plastic system may be more appropriate to speculate about the interaction of neural systems and how these systems change across tasks and time.

Although this study attempts to quantify risk behaviors in developing adolescents, the limitation of our analysis is that some of our parameters vary from previous studies. Prior work evaluating risk behaviors and neural activation incorporated cross-sectional and longitudinal, analyses differing across parameters in task and definition of risk. For example, in cross-

sectional samples, while Benningfield et al. (2014) examined the association between discounting (as measured by Monetary Choice Questionnaire) and differences in activation to big, small and neutral rewards, Claus et al. (2018) examined the moderating effect of substance use on the association between brain activation and risk-taking tendencies on the Balloon Analogue Risk Task (BART). Further, in longitudinal analyses of adolescent risk behaviors, whereas Qu et al. (2015) explored the mediating effect of ventral striatal activation on the association between parent-child relationships and risk-taking on the BART, Braams, van Duijvenvoorde, Peper, & Crone (2015) examined associates between changes in nucleus accumbens response during a Two Choice task (heads or tails) and risk performance as captured by the BART and self-report measure of Behavior Inhibition System/Behavior Action System. Not surprisingly, due to variability in definition of risk and parameters, results varied from study-to-study.

Importantly, our results do not capture age related change that is represented in the neurodevelopmental models. This study focused on variation across risk profiles, both cross-sectionally and longitudinally, to determine whether this variability can be explained by neural activation that has been posited in previous models. Activation in adolescent risk profiles, in this analysis, cannot be attributed either of the developmental models. The age-related trends may still be evident in the models, but the heuristics may not necessarily provide the evidence necessary to explain adolescents that do and do not engage risk behaviors, as was previously suggested (Spear, 2000)

Conclusion

Overall, although parameter selection in this study varied from previous studies and a focal age-range was used, this is the first study to our knowledge to examine differences in

623 neural activation across real-world risk profiles (from multiple waves) in adolescents. The results
624 in this study demonstrate that the previous hypothesized models cannot explain the variation in
625 risk profiles, and whole brain differences may depend on how risk profiles are defined.
626 Moreover, common hot spots of reward related research, such as the ventral striatum, do not
627 differentiate general risk profiles in adolescents. This posits an important reassessment of how
628 risk is captured and modeled in the developing adolescent brain, in order to improve predictive
629 utility and use in interventions.
630

631 Table 1: Demographic characteristics and behavioral performance of full sample completing the Monetary Incentive Delay Task by Risk Profile

	Average <i>n</i> = 63	High <i>n</i> = 41	Total <i>n</i> = 104	Effect Size
Sex, Female <i>n</i> (%)	37 (62.7)	22 (37.3)	59 (56.7)	$\Phi = .02$
Race, <i>n</i> (%)				
Black, non-Hispanic	12 (19.0)	3 (7.3)	15 (14.4)	
White, non-Hispanic	40 (63.5)	34 (82.9)	74 (71.2)	
Other	5 (8.0)	1 (2.4)	6 (5.7)	
Hispanic/Latinx	6 (9.5)	3 (7.3)	9 (8.7)	
	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	
Age	18.6 (1.3)	19.3 (1.4)	18.9 (1.3)	$d = .52^{**}$
Parental Education	4.4 (1.1)	4.1 (1.2)	4.3 (1.2)	$d = .26$
BMS	-0.28 (0.1)	0.83 (0.8)	0.16 (0.6)	$d = 1.95^{***}$
WASI IQ	106.1 (12.2)	101.1 (11.7)	104.0 (12.2)	$d = .41^*$
Overall Acc. %	57.4 (3.2)	56.2 (3.1)	56.9 (3.2)	$d = .38$
Win Big	63.7 (9.2)	61.2 (9.1)	62.7 (9.2)	$d = .27$
Win Small	56.8 (9.5)	59.3 (9.7)	57.8 (9.6)	$d = .26$
Neutral	49.8 (14.2)	44.5 (14.5)	47.7 (14.5)	$d = .37$
Lose Small	56.3 (9.5)	56.5 (7.7)	56.4 (8.8)	$d = .02$
Lose Big	60.2 (10.5)	59.4 (10.4)	59.9 (10.4)	$d = .08$
MRT (ms)	296.5 (24.4)	299.8 (19.5)	297.9 (21.9)	$d = .15$
Win Big	293.4 (22.9)	297.4 (21.0)	295.0 (22.1)	$d = .18$
Win Small	296.4 (26.4)	300.5 (19.5)	298.1 (23.9)	$d = .18$
Neutral	300.4 (28.3)	302.3 (21.8)	301.2 (25.8)	$d = .08$
Lose Small	296.1 (24.5)	301.3 (22.8)	298.1 (23.9)	$d = .22$
Lose Big	296.8 (23.7)	298.3 (21.8)	297.4 (22.9)	$d = .07$

632 BMS = Behavioral Misadventure Score; WASI IQ = Wechsler Abbreviated Scale of Intelligence; Parental
633 Education: 1 = grade school or less, 2 = Some High School, 3 = Completed High School, 4 = some
634 college, 5 = completed college, 6 = graduate or professional school. Acc = Accuracy; MRT = Mean
635 response time; ms = milliseconds; d = Cohen's d
636 $p < .05^*$, $p < .01^{**}$, $p < .001^{***}$

Table 2: Whole Brain Analyses: significant differences in activation for Average (N= 63) and High (N = 41) Risk-taking adolescents to anticipation of reward

Cluster Index ^a	Cluster peak x, y, z	# of Voxels	Cluster Label ^b	<i>p</i> [*]
14	-15, -3, 16	722	Left-Caudate	.03
13	22, -62, -16	208	Right Cerebellar	.03
12	16, -82, 4	129	Right Primary Visual	.04
11	-22, -72, 2	70	Left Primary Visual	.04
10	-17, 23, 12	44	^c Left-Caudate Nucleus	.04
9	6, -74, 10	36	Right Primary Visual	.04
8	-10, -60, 50	36	Left Precuneus	.04
7	18, -36, 34	25	^c Posterior Cingulate	.04
6	-16, -50, -8	22	Left-Secondary Visual	.04
5	34, -30, 28	19	^c Right Operculum	< .05
4	4, -40, 42	17	Posterior Cingulate	< .05
3	-4, -32, 62	11	Primary Motor	< .05
2	-4, -72, -2	10	Left Visual	< .05
Cluster Index ^a	Cluster peak x, y, z	# of Voxels	Cluster Label ^b	<i>p</i> [#]
8	30, 32, 34	214	Right Dorsolateral Prefrontal Cortex	.052
7	20, -6, 58	50	Right Premotor	.072
6	4, 20, 40	47	Paracingulate Gyrus	.069
5	10, -68, 52	33	Right Precuneus	.074
4	-6, -60, 48	30	Left Precuneus	.066
3	-12, -2, 18	16	Left Caudate	.071
2	12, 8, 52	9	Right Supplementary Motor	.078
1	36, 6, 26	3	Right Precentral Gyrus	.078

^a Cluster index identified using fsl command *cluster* that identified peak clusters in volume, index 1 not reported due to number of voxels = 1, clusters plotted on MNI brain in Figure 1 and Figure 2.

^b To identify region for cluster label, we used a combination of reverse inference on neurosynth.org/locations to identify top association with cluster activation and cross-referenced with *FSL Harvard-Oxford Cortical Structural Atlas* (percent association provided in superscript).

^c Implies regional association, due to peak being in white matter.

^{*} Probability $\alpha < .05$ used to threshold results of TFCE output from randomise

[#] Lowered $\alpha < .08$ used to threshold results of TFCE output from randomise (< .05, results null)

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 649 *Figure 1.* Whole Brain Permutation Wave 1: Average > High Risk Taking Profile during
 650 anticipation of Big win vs Neutral contrast, thresholded $p < .05$
 651 Non-permutation test includes 5000 permutations, using FSL *randomise* with threshold-free cluster
 652 enhancement. Statistical maps thresholded at lower value .05 – clusters selected from Table 1.

Figure 2. Whole Brain Permutation Longitudinally Stable Average > High Risk Taking during anticipation of Big win vs Neutral contrast, thresholded $p < .08$
 DLPFC = Dorsolateral prefrontal cortex. Non-permutation test includes 5000 permutations, using FSL *randomise* with threshold-free cluster enhancement. Statistical maps thresholded at lower value, $p < .08$, thresholding at .05 provided no significant differences – clusters selected from Table 1.

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