Longitudinal changes in brain structures related to appetitive reactivity and regulation across development

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ABSTRACT

In the United States over one-third of the population, including children and adolescents, are overweight or obese. Despite the prevalence of obesity, few studies have examined how food cravings and the ability to regulate them change throughout development. Here, we addressed this gap in knowledge by examining structural brain and behavioral changes associated with regulation of craving across development. In a longitudinal design, individuals ages 6–26 completed two structural scans as well as a behavioral task where they used a cognitive regulatory strategy to decrease the appetitive value of foods. Behaviorally, we found that the ability to regulate craving improved with age. Neurally, improvements in regulatory ability were associated with cortical thinning in medial and lateral prefrontal cortex. We also found that models with cortical thickness measurements and age chosen by a lasso-based variable selection method could predict an individual's regulation behavior better than age and other behavioral factors alone. Additionally, when controlling for age, smaller ventral striatal volumes were associated with higher body mass index and predicted greater increases in weight two years later. Taken together, these results demonstrate a role for structural brain changes in supporting the ability to resist cravings for appetitive foods across development.

1. Introduction

Obesity is a major public health concern, with over a third of children and adolescents in the United States labeled as overweight or obese (Lobstein et al., 2015; Ogden et al., 2014). The ability to resist or redirect cravings for appetizing but unhealthy foods is critical in maintaining a normative weight. Failures to appropriately regulate such cravings can lead to excess weight and obesity, which over time may contribute to heart disease, stroke, and diabetes (Flegal et al., 2012; Ogden et al., 2014). Given these risk factors, it is surprising that only a handful of studies have examined the relationship between brain development and craving (Batterink et al., 2010; Giuliani and Pfeifer, 2015; Silvers et al., 2014; van Meer et al., 2016; Yokum and Stice, 2013), and none of these studies have been longitudinal in design. Furthermore, no former studies have assessed how the structure of neural regions associated with regulation of craving change with age.

Two types of brain systems are strongly implicated in the regulation of craving in adults. The first *reactivity* system is thought to support

appetitive responses to food and includes the ventral striatum (VS), a subcortical area implicated in assessing the reward value of stimuli. The second *regulation* system is thought to support the cognitive control of affective impulses and includes ventrolateral prefrontal cortex (vlPFC), ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), anterior cingulate cortex (ACC) and parietal lobe (Giuliani et al., 2018, 2014; Kober et al., 2010; Siep et al., 2012).

While no studies linking brain structure to regulation of craving exist, prior cross-sectional functional magnetic resonance imaging (fMRI) studies on regulation of craving and brain *function* across development found that adolescents and children – as compared to young adults – showed weaker vlPFC and dlPFC activation coupled with greater VS activation and self-reported craving (Giuliani and Pfeifer, 2015; Silvers et al., 2014; Yokum and Stice, 2013). These data suggest that interactions between appetitive reactivity and regulation neural systems change functionally across development.

Prior work also suggests that these regions change structurally

across development. For example, VS undergoes reductions in volume and connectivity to cortex during development (Fareri et al., 2015; Raznahan et al., 2014). Frontoparietal networks implicated broadly in self-control show a protracted developmental trajectory relative to subcortical structures associated with appetitive and emotional responding (Casey, 2015; Mills et al., 2014a,2014b). However, while it is known that PFC undergoes dramatic structural changes across development (Gogtay et al., 2004; Lenroot and Giedd, 2006; Sowell et al., 2004), the effects of these changes on appetitive reactivity (i.e. cravings for food) and regulation remain to be discovered.

While a large body of work exists demonstrating that neural structures change robustly from childhood to adulthood, to date, there are no longitudinal MRI-based studies linking these changes to behavioral measures related to food craving and its regulation. To address this gap in knowledge, we used a cross-lagged longitudinal design to determine 1) whether and how behavioral markers of craving and its regulation change with age; 2) whether and how changes in these behavioral markers relate to structural changes in brain systems implicated in appetitive reactivity and regulation; 3) which set of neural structures and individual differences factors best predicted an individual's regulation behavior, and 4) the extent to which a real world index of being overweight or obese - body mass index (BMI) - is associated with craving, regulation, and brain structure during development.

Participants ages 6–26 were scanned at two time points approximately two years apart and completed a food craving regulation task in which craving was measured using participants' ratings of how much they wanted to eat a series of appetizing unhealthy foods. We tested whether age predicted changes in cravings for those foods and the ability to regulate them, and assessed the role of structural brain maturation in influencing such changes.

2. Methods

2.1. Participants

The individuals in this study represent a subset of participants from a previously published cross-sectional functional MRI study (Silvers et al., 2014), and our sample size consisted of those individuals who returned for the two year follow-up and had complete behavioral and imaging data. Fifty-three healthy individuals ages 6–23 participated in the initial experiment and returned approximately two years later for retesting (Fig. 1, mean time elapsed between scans = 2.07 years, SD = .47 years). Four participants were excluded either due to excessive head motion in the scanner or not completing the task, leaving a total of sample of 49 individuals (mean age = 15.08, SD = 4.95, 32 female). Participants were recruited from the New York City
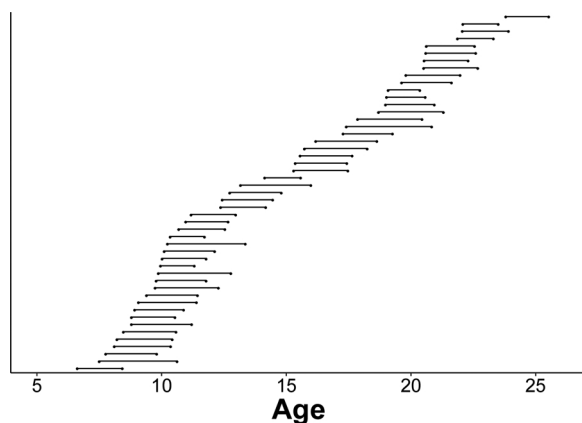

Fig. 1. Age and duration of scan interval for each participant. Each row represents a participant, each dot represents their age at time of scan, and each line represents the duration between scans.

metropolitan area and were pre-screened for psychiatric, developmental, and eating disorders prior to participating in the experiment. The Columbia University Institutional Review Board approved the study and all participants gave informed consent.

2.2. Task

Participants completed a regulation of craving task (Kober et al., 2010; Silvers et al., 2014) that included 40 trials in which images of appetitive energy dense foods were presented (Fig. 2). Food images were downloaded from public online sources, and pilot testing on a separate sample of children, adolescents, and adults indicated that all depicted foods were rated as highly desirable. Care was taken to ensure a variety of food types were represented with an equivalent representation of both sweet and salty foods.

Each trial began with a cue word (Close or Far) shown for 2 s. Close trials assessed appetitive reactivity to the food stimuli by instructing participants to imagine the food being directly in front of them and to think about its appetitive features including how it might smell and taste. Far trials assessed regulation of craving by instructing participants to use a distancing reappraisal strategy (Silvers et al., 2012) where they were told to imagine the food was far away and to think about its perceptual features, such as the color or shape. Following the cue, participants viewed the food picture for eight seconds, and after a jittered fixation period of approximately 3 s, used a five-point scale to rate how much they wanted to eat the foods. Prior to doing this task in the scanner, participants were trained using a short practice version of the task in order to become comfortable with using the strategies (see Silvers et al., 2014 for more details about training).

Twenty trials were assigned to the reactivity condition (Close) and twenty were assigned to the regulation condition (Far). The order of conditions and assignment of pictures was counterbalanced across participants.

2.3. Age calculation

Age at each time point was calculated as the date of scan minus the date of birth divided by the number of days in a year accounting for leap years (365.25). Age terms were not rounded in analyses. Age was plotted continuously and rounded up to the nearest whole number in figures for visualization purposes.

2.4. Body mass index

After the scan, participants' height and weight were measured. Body mass index (BMI) percentile was calculated for all participants using the Center for Disease Control's BMI-for-age growth chart (Kuczmarski et al., 2002). BMI percentile is considered a more accurate measure of body composition in children than BMI (Mei et al., 2002), and is only normed for individuals under the age of 20. Thus, for continuous assessments of BMI percentile, we excluded adult participants twenty years and older. The total sample for continuous analyses in Time 1 was 40 (mean age = 12.57, SD = 4.09, 26 females) and 33 for Time 2 (mean age = 13.25, SD = 3.0, 19 females). To be able to compare BMI across all participants with BMI measurements, we assigned each participant to a weight status category as provided by the CDC for BMI percentile in individuals under age 20, and BMI measurements for individuals over age 20 (categories = underweight, normal weight, overweight, obese). More details of BMI methods and results are described in supplemental text.

2.5. Behavioral data acquisition

Stimuli were presented using E-Prime 1.0 (Psychology Software Tools, Inc., https://pstnet.com/). Participants viewed images by looking at a mirror located above the head coil that reflected a projector
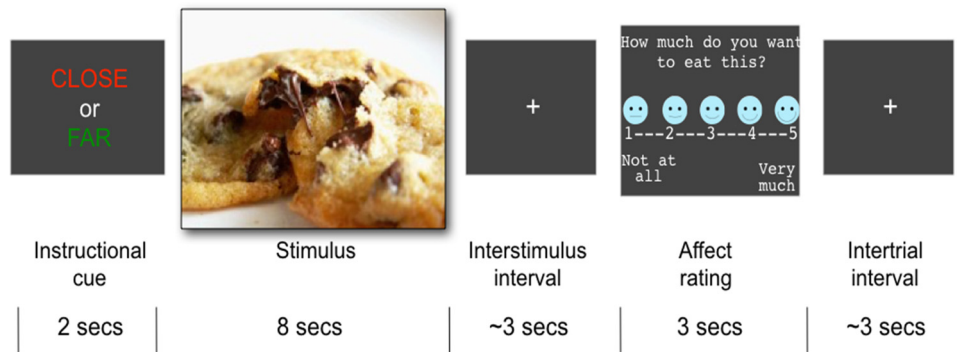
Fig. 2. Trial structure for the Regulation of Craving task. 1. On each trial a cue indicated which strategy participants should use when viewing the food stimulus. Close cue indicates reactivity trials, and Far cue indicates regulation trials. 2. Participants view the stimulus. 3. Participants rate their craving for the food.

located just outside the scanner bore.

2.6. Imaging data acquisition

We acquired structural images on a 3 T Siemens Magnetom Trio scanner using a high resolution T1-weighted MPRAGE sequence with a repetition time of 2170 ms, an echo time of 4.33 ms, and 120 1.5 mm slices. All structural analyses were conducted using this sequence.

2.7. MRI preprocessing

MPRAGE scans were reconstructed using Freesurfer v5.3.0 (Fischl et al., 2002, 2004). Images were then processed through Freesurfer's longitudinal processing stream (Reuter et al., 2010, 2012). Processing streams are described in detail in the above citations. After each reconstruction, data were visually assessed by two trained inspectors and minor edits were made as needed. We excluded scans with movement-based artifacts (Ducharme et al., 2016). The volume-based longitudinal stream was used to calculate grey matter volume in subcortical regions, and we used measurements from the cross-sectional stream to estimate intracranial volume (ICV), one of our control metrics (Mills et al., 2016). The surface-based longitudinal stream was used to calculate grey matter cortical thickness, which is the distance between white matter and the pial surface.

2.8. Behavioral data analyses

We used lme4 and lmerTest using the statistical software language, R, to run multilevel regression models on trial-by-trial ratings, nested by participant to assess contributions of age and cortical thickness to changes in appetitive reactivity and regulation within and between participants (Bates et al., 2014; Kuznetsova et al., 2013; R Core Team, 2014).

In models assessing rate of change by year (annualized change) our explanatory variable was age at Time 1 and the outcome variable was the difference in rating from Time 2 to Time 1 divided by the time elapsed between scans. Annualized change measurements were used to account for the variance in the distance between scan sessions across participants.

To account for baseline individual differences in reactivity during regulation trials, we calculated an average reactivity score by taking the mean rating in the reactivity condition for each participant during each phase. This average reactivity score was used as a control predictor in indicated behavioral and structural analyses.

2.9. Structural imaging analyses

We used two complementary analytic methods to assess if and how changes in brain structure related to changes in regulation of craving

with age. A vertex-wise whole brain general linear model (GLM) approach located regions of interest (ROIs) most closely associated with age and regulation of craving. A lasso-based brain-as-predictor approach (described in section 2.9.3) on ROIs from an automated Freesurfer atlas was applied to determine which combined neural and behavioral factors were most predictive of one's ability to regulate craving.

2.9.1. Whole brain surface analyses

We conducted the vertex-based whole-brain cortical surface analyses in Freesurfer 5.3 using the longitudinal two-step procedure in mri_glmfit. Surfaces were resampled to a common space (fsaverage) and smoothed with a 15-mm full-width half maximum kernel. GLMs were used to test the relationship between cortical thickness, craving, regulation, and age. Whole-brain analyses were corrected for multiple comparisons using Monte Carlo simulations with a cluster-forming threshold of $p < .0001$, and cluster-wise $p = .05$ (Hagler et al., 2006). We controlled for gender in these analyses because we had greater representation of females in our sample, and because of observed differences in thickness and maturational timing between males and females across development (Giedd and Rapoport, 2010; Goddings et al., 2014; Mutlu et al., 2013). Given the longitudinal design of this study and surface-based methods used, we believe that we are adequately powered to detect changes in cortical thickness within subjects given our sample size (Mills and Tamnes, 2014).

2.9.2. Region of interest analyses

We extracted cortical thickness values from each significant cluster from the whole-brain regulation of craving GLM. We then ran a series of multilevel models with linear, quadratic, and cubic age terms to assess which model best described the shape of change in cortical thickness of these regions with age.

Because subcortical regions are not included as part of the whole brain cortical surface analysis in Freesurfer, we also conducted another multilevel regression analysis assessing the volume of an a priori subcortical region (taken from Freesurfer's volume-based longitudinal processing stream) associated with craving reactivity - ventral striatum - and its relationship with craving, regulation, and BMI. Models with and without intracranial volume (ICV), whole brain volume (WBV), and gender are reported in supplemental text (for discussion on using brain volume proportions or covariates see Mills et al., 2016 and Tamnes et al., 2017).

2.9.3. Predictive models of age, gender, BMI, and cortical thickness on self-reported regulation of craving

In this analysis, we used a brain-as-predictor approach (Berkman and Falk, 2013; Doré et al., 2017; Telzer et al., 2018) to identify which brain regions and individual difference factors, such as age and gender, were most important in predicting what an individual's regulation

rating would be for each trial in the experiment. The neural measures in these predictive models consisted of the cortical thickness estimates of ROIs from the Desikan-Killiany-Tourville (DKT) atlas, an automated, anatomically-derived cortical parcellation with 31 regions per hemisphere (Desikan et al., 2006; Klein and Tourville, 2012). These atlas regions were used in order to reduce dimensionality of the neural measures from 150,000 vertices per hemisphere, and also to maintain independence from the clusters extracted from the vertex-based GLM results (Vul et al., 2009). Predictors included the 62 DKT atlas-based ROIs, age, gender, average reactivity score, and BMI group. The outcome variable was the self-reported craving rating made by each participant after viewing each food image in the regulation condition.

For the first step of this modeling procedure, we used glmnet in R to run a least absolute shrinkage and selection operator (lasso) regression (Friedman et al., 2018; Tibshirani, 1996). The lasso performed variable selection to select predictive ROIs and provided estimates of predictive accuracy in models of the contribution of age, reactivity score, and cortical thickness to trial-by-trial regulation ratings. Lasso regression uses an L1 penalty to reduce multicollinearity among predictors, prevent overfitting, and perform variable selection by shrinking the coefficients toward zero, thus increasing model stability and improving predictive accuracy. The amount of shrinkage, and thus the number of variables that are selected to be included in the model, are controlled by a hyperparameter, lambda. We employed k-fold cross-validation to determine the optimal lambda which was the one that resulted in the lowest cross-validated mean squared error (MSE). This method is beginning to gain traction in neuroimaging research, and has been used in functional imaging studies for voxel selection and in structural imaging studies to construct a "brain maturation index" of lasso-selected ROIs (Cao et al., 2015; Chang et al., 2015; Cribben et al., 2012).

For the second step of this procedure, we used lme4 and rsample in R to compare several multilevel model formulations: the full lasso-derived model with the selected ROIs and individual difference factors; a reduced behavior-only model that only included age and individual difference factors identified by the lasso but not ROIs; a brain-only model that did not include age as a predictor; and a null model that included no predictors (Kuhn and Wickham, 2017). All models used regulation rating as the outcome variable. The models were compared using k-fold cross-validation to determine the model with the lowest MSE.

3. Results

3.1. Behavioral results

3.1.1. Changes in reactivity and regulation of craving with age

We found that self-reported craving from Time 1 to Time 2 in both reactivity trials, $b = -.04$, $se = .01$, $t(47) = -2.75$, $p = .007$, and regulation trials, $b = -0.09$, $se = .01$, $t(47) = -5.48$, $p = 1.08 \times 10^{-6}$, decreased with age. When controlling for baseline reactivity, we found an even stronger effect of age on regulation rating, $b = -0.09$, $se = .01$, $t(46) = -6.49$, $p = 4.21 \times 10^{-9}$; likelihood ratio test between age only and age plus reactivity model: $\chi2 = 46.90$, $df = 1$, $p = 7.45 \times 10^{-12}$. These models showed linear decreases with age with both reactivity and regulation trials, and quadratic and cubic age terms did not improve model fit. We found a main effect of condition such that participants reported less craving in the regulation condition compared to the reactivity condition $b = -.75$, $se = .09$, $t(47) = -7.65$, $p = 7.39 \times 10^{-10}$. We found a condition by age interaction such that older individuals reported lower cravings in the regulation condition than the reactivity conditions compared to those younger in age $b = -.05$, $se = .01$, $t(46) = -2.77$, $p = .007$ (Fig. 3).

3.1.2. Rates of change in reactivity and regulation with age

Rate of change from Time 1 to Time 2 did not differ as a function of age (Fig. 4) suggesting that decreases in craving, and improvements in

regulation ability, changed at a steady rate across the age range: age at Time 1 predicting annualized change in reactivity $b = .007$, $se = .01$; $t(47) = .70$, $p = .48$, age at Time 1 predicting annualized change in regulation $b = -0.01$, $se = .01$, $t(47) = -0.83$, $p = .40$. We also did not find that rate of change differed with age in the regulation condition when controlling for average reactivity at Time 1, $b = -0.01$, $se = .01$; $t(46) = -1.38$, $p = .17$.

3.2. Imaging results

3.2.1. Main effect of reactivity and regulation of craving on cortical thinning

In the vertex-wise GLM analysis, self-reported craving was not associated with cortical thinning. In contrast, better regulation of craving correlated with cortical thinning in the rostral ACC, dmPFC, dlPFC, vlPFC, inferior parietal lobe, and postcentral gyrus (Fig. 5; Supplemental Table 1). When including age as a covariate to assess whether thickness-regulation associations were age-dependent or age-independent, no cluster-corrected ROIs remained significant at the whole-brain level. This suggests that changes in regulation of craving are highly interrelated with changes in age. Visualization and cluster table of vertex-wise GLM analysis of the relationship between age and cortical thickness are available in Supplemental Table 2 and Supplemental Fig. 1.

3.2.2. ROI analysis of longitudinal age-related changes in brain regions associated with reactivity and regulation of craving

Cortical thickness values of all clusters extracted from the regulation of craving contrast were all correlated with age (min $r = -0.46$, $p = 1.27 \times 10^{-6}$, max $r = -.68$, $p = 1.99 \times 10^{-14}$; Fig. 6). Linear growth trajectories in the relationship between age and thickness were the best fit for all ROIs: dlPFC: $b = -.02$, $se = .005$, $t(47) = -5.40$, $p = 6.15 \times 10^{-7}$, dmPFC: $b = -.02$, $se = .004$, $t(47) = -7.32$, $p = 7.47 \times 10^{-11}$, rostral ACC $b = -.03$, $se = .006$, $t(47) = -5.66$, $p = 2.67 \times 10^{-7}$, vlPFC: $b = -.02$, $se = .004$, $t(47) = -5.71$, $p = 1.54 \times 10^{-7}$. Supplemental Fig. 2 shows visualizations of the relationship between regulation of craving ratings and cortical thickness in these four ROIs.

3.2.2.1. Ventral striatum volume.
VS volumes did not correlate with craving or regulation of craving. Bilateral VS volumes were modestly associated with age where increases in age were related to decreases in VS volume, Left: $b = -.04$, $se = .02$, $t(47) = -2.24$, $p = .02$, Right $b = -0.04$, $se = .02$, $t(47) = -2.04$, $p = .04$ (Fig. 7). A linear trajectory was the best fit in these models.

3.3. Best-fit models in predicting regulation of craving ability

Individual regulation of craving ratings were best predicted by a model including age, average reactivity rating, plus the thickness values of 23 of the 62 available regions. Regions selected from the lasso included a number of the regions implicated in regulation of craving found in the vertex-wise GLM as well as a selection of ROIs distributed across the entire brain (Supplemental Fig. 3A). Cross-validated MSE from full, reduced, and null model comparisons indicated that models with age plus the selected cortical thickness regions while controlling for average reactivity rating performed best: null model MSE: 1.35, age only model MSE: 1.28, brain only model MSE: 1.20, age plus brain model MSE: 1.19 (Supplemental Fig. 3B; note that all models except the null model include the average reactivity rating as a nuisance regressor). A likelihood ratio test model comparison between the age only model and brain plus age model converged with the MSE results suggesting that inclusion of measures of cortical thickness are better predictors of regulation behavior than age alone: $\chi2 = 79$, $df = 22$, $p = 2.36 \times 10^{-8}$. Likelihood ratio tests also showed that the brain only model and age plus brain model were statistically different $\chi2 = 13.94$, $df = 1$, $p = .0001$. BMI group and gender did not improve model fit.
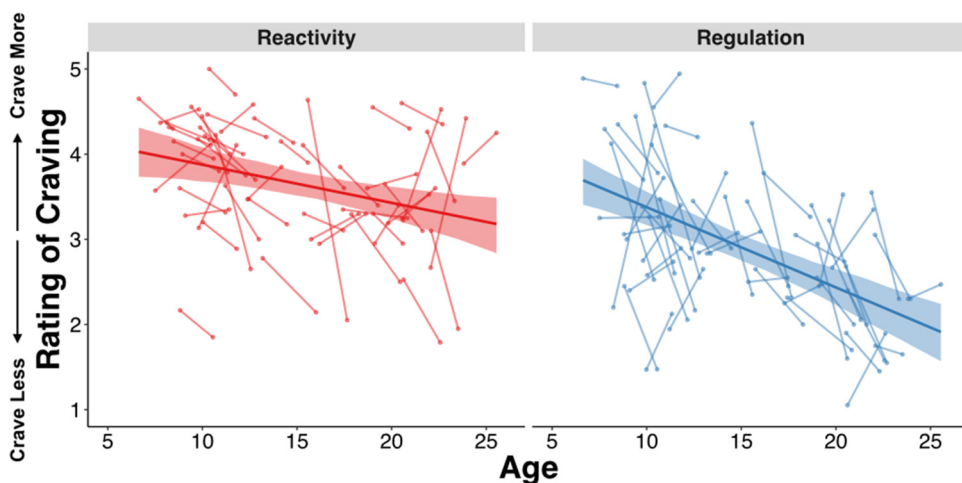
Fig. 3. Behavioral results for Regulation of Craving task. Both reactivity and regulation ratings decreased with age, with regulation ratings showing steeper decreases. Each line joined by two dots represents one participant and their age at the time of each scan. Lower ratings = lower craving. Regression line represents fixed effects estimate and grey band represents the 95% confidence interval.

3.4. Effects of body mass index

BMI Group was not related to self-reported craving or its regulation: reactivity: $b = -0.20$, $se = .15$, $t(47) = -1.35$, $p = .17$., regulation: $b = -0.09$, $se = .19$, $t(47) = 4.87$, $p = .63$.

We did find, a small effect such that regardless of age, overweight and obese individuals had smaller VS volumes compared to healthy and underweight individuals, Left VS: $b = -0.37$, $se = .13$, $t(46) = -2.78$, $p = .01$, Right VS: $b = -0.23$, $se = .11$, $t(46) = -1.97$, $p = .05$ (Fig. 7B). Additionally, in the sample of individuals with complete BMI percentile scores (n = 27), we found that heavier individuals with smaller VS volumes were more likely to gain weight from Time 1 to Time 2 compared to leaner individuals, Left VS: $b = -0.14$, $se = .08$, $t(22) = -1.71$, $p = .1$, Right VS: $b = -0.22$, $se = .05$, $t(22) = -3.85$, $p = .0008$.

BMI Group was not associated with cortical thinning in the vertex-wise analysis, nor did it improve model fit in the lasso-based ROI analyses predicting regulation of craving. More BMI results can be found in the supplemental materials.

4. Discussion

This is the first study to investigate longitudinal changes in brain structures associated with regulation of craving across development. This work revealed four key findings about how reactivity and regulation of appetitive cues change with age and relate to neural structure. First, we showed that both reactivity to appetitive foods and the ability to regulate that reactivity changed with age. Second, we found that improved regulation of craving was associated with late maturing lateral and medial prefrontal cortex thinning. Third, we discovered that predictive models including a combination of age and cortical thickness measurements distributed throughout the brain best predicted regulation of craving ratings over simply age alone. Finally, we determined that lower VS volume was associated with higher BMI and a greater likelihood of weight gain at Time 2. These findings have implications for basic and translational research on obesity as well as reward processing and its regulation across development.

Behaviorally, we found that craving decreased linearly with age. Regulation of craving abilities improved and also changed linearly with age, to a greater extent than age-related decreases in craving. While the extant prior cross-sectional developmental studies of appetitive regulation did not find stronger improvements in regulation abilities with age relative to craving (Giuliani and Pfeifer, 2015; Silvers et al., 2014), this study's findings do replicate a number of prior studies that showed age-related improvements in implementation of regulation strategies while viewing negative emotional pictures (McRae et al., 2012; Silvers et al., 2016, 2012). Notably, while all these studies varied in the degree to which reactivity and regulation of affective cues (be they appetitive or aversive stimuli) changed with age, all found at least modest age-related decreases in reactivity and all but one (Giuliani and Pfeifer, 2015) found improvements in regulation with age.

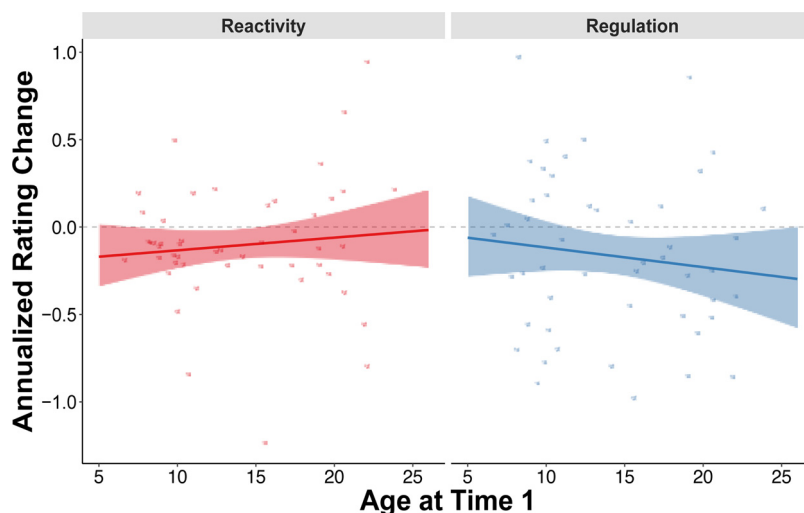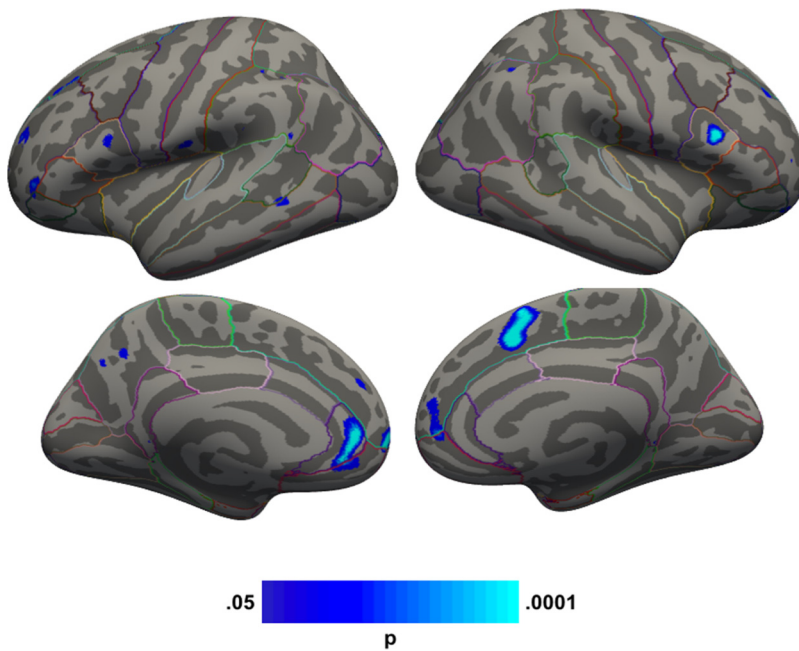Based on prior literature of appetitive behaviors (e.g. Barkley-

Fig. 4. Annualized change in reactivity and regulation by age at Time 1. Rate of change in behavior did not. significantly vary by age.

Fig. 5. Main effect of regulation of craving on cortical thinning. Brain images show clusters where improved regulation ability was associated with greater thinning. Gender was included as a nuisance regressor. Results were corrected for multiple comparisons by simulation-based clusterwise correction. Cluster statistics shown in Supplemental Table 1.

Levenson et al., 2013; Galvan, 2010; Somerville et al., 2010) we hypothesized that we might find a non-linear peak in reactivity during adolescence. We did not find this pattern, which may be for a few reasons: first, in the cross-sectional functional imaging study conducted in our lab with the Time 1 data (Silvers et al., 2014), we found that reactivity in this task followed a linear trajectory. The only other study using a similar food-based appetitive task in a continuous developmental sample of children through adults also observed only linear changes with age (Giuliani and Pfeifer, 2015). Second, while non-linear reactivity effects have been demonstrated in other functional imaging studies of appetitive and/or reward-based behaviors, these effects have not been consistently observed in those studies' behavioral results (Davidow et al., 2018; Rosenbaum and Hartley, 2019). One possible reason for these inconsistencies is that many of the papers that find heightened adolescent reward behavior only compare adolescent and adult samples and exclude child samples (Li, 2017) making it difficult

to determine if behavioral changes are following a linear or non-linear pattern. Third, in prior literature, appetitive reactivity was measured in qualitatively different ways in both stimuli type (e.g. happy faces and money) and rating scales (e.g. binary, continuous scale, or discrete choices). Appetitive reactivity may look different in different appetitive domains, and primary rewards such as food cues may not elicit the same type of response as a happy face. To resolve these discrepancies, more longitudinal developmental studies on appetitive reactivity and regulation are needed to determine if the observed differences between our findings and those of the previously mentioned studies may be attributed to inherent differences between cross-sectional versus longitudinal designs, age range differences, variation in task design and assessment, or type of appetitive stimuli used during the task.

While craving decreased with age, we did not find a relationship between craving and cortical thinning. Regulation of craving, however, was associated with cortical thinning in lateral and medial prefrontal
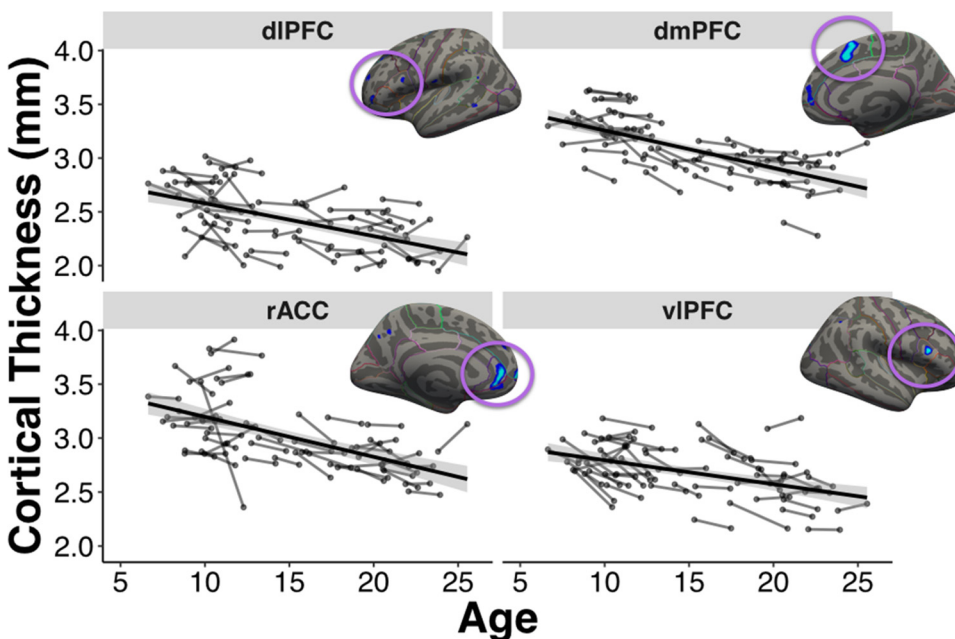
Fig. 6. Changes in thinning in regulation of craving clusters across age. Regression line represents fixed effects estimate and grey band represents the 95% confidence interval. Clusters shown are largest non-repeating clusters found in contrast (2 per hemisphere) and are left dlPFC, right dmPFC left rostral ACC, right vlPFC. See Supplementary Table 1 for complete list of regions and statistics.
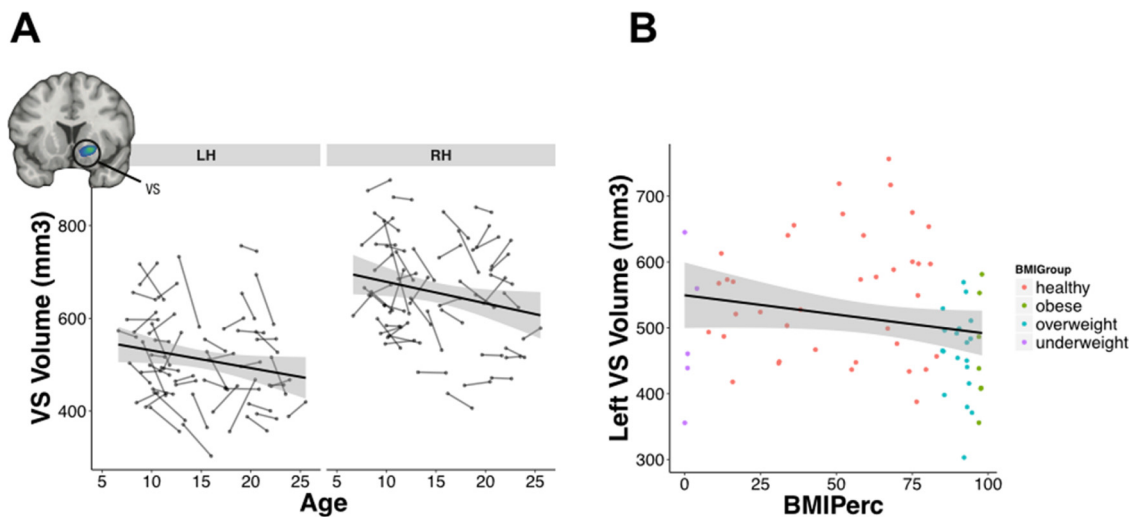
Fig. 7. Relationship between ventral striatum volumes, age, and BMI group. **A.** Left (LH) and right (RH) VS volumes showed linear decreases with age. **B.** Controlling for age, left and right VS volumes were smaller in overweight and obese individuals in both Time 1 and Time 2.

regions associated with emotion regulation and cognitive control (Buhle et al., 2013; Crone and Steinbeis, 2017). The findings from this work converge with cross-sectional functional MRI research on craving and its regulation in both developmental and adult samples (Giuliani et al., 2014; Giuliani and Pfeifer, 2015; Silvers et al., 2014). The structural changes in these regions were highly correlated with age suggesting that associations between thinning and appetitive regulation are largely age-dependent. This finding is supported by prior work on brain structure changes across age and its relationship to other cognitive control mechanisms such as inhibition and working memory (Kharitonova et al., 2013; Tamnes et al., 2013). While we cannot determine whether the relationship between craving regulation and cortical thinning we observed differs from other types of regulation and cognitive control, we can say that given the lack of a relationship between craving and cortical thinning, that the brain-behavior relationships in the measures we used differ. Future work could assess the domain generalness or specificity of multiple types of regulation and their relationship with developmental changes in brain structure.

From our a priori ROI analysis of VS, we found that older age was associated with smaller bilateral VS volume which is consistent with prior studies of subcortical volume changes (Østby et al., 2009; Raznahan et al., 2014). All structural regions we measured followed a linear trajectory in the degree to which they changed with age, which is consistent with other longitudinal structural papers reporting changes in thickness and volume in children as young as eight years old (Mills et al., 2014a,2014b; Tamnes et al., 2017). While we did not observe nonlinear changes in brain structure with age, larger samples and more than two time points are needed to get the most replicable and reliable estimates of cortical thickness and volume change patterns (Shaw et al., 2008).

The lasso-based ROI brain-as-predictor analysis complemented the whole-brain results by showing the best-fit model in predicting regulation of craving ratings at each trial. These results determined in a data-driven way, that neural structure in combination together with age is a better predictor of behavior than the behavioral results could supply alone. One interpretation of these results is that inclusion of the selected neural regions with age formed a richer, more granular index of maturity than age or other behavioral measures could provide by themselves. Several frontoparietal regions found in the whole brain results were selected in the lasso model, however, a range of posterior and temporal regions contributed to the model as well. This finding supports the theory that a more distributed network of brain regions may influence behavior more than standard, highly thresholded univariate GLM approaches can show. A limitation of this approach is that

the ROIs used from the automated atlas were large relative to the clusters that came out of the whole brain GLM; use of an atlas with smaller parcellations and a greater number of regions could yield different results. Thus, similar to other predictive imaging methods like multivoxel pattern analysis, use of the lasso as implemented here may be more suited for prediction of behavior rather than brain-mapping. Development of this method could prove to be useful in diagnostics of normative and non-normative brain development and/or behaviors, and could work in tandem with approaches using functional imaging methods to accomplish this goal (e.g. Dosenbach et al., 2010).

Finally, we found that bilateral VS volume was associated with individual differences in BMI. Heavier individuals had smaller VS volumes on average. While this pattern has not been consistently found in VS, a general association of higher BMI and lower brain volume in other cortical and subcortical regions has been observed in children and adults (Brain Development Cooperative Group, 2012; Marqués-Iturria et al., 2013; Raji et al., 2010). We also found that heavier individuals at Time 1 with smaller VS volumes were more likely to have gained weight at Time 2. This suggests that low VS volumes could be a specific neural marker for future weight gain, though, future work would need to replicate this finding with larger samples, and the causal pattern of BMI and low VS volume would need to be established. We did not find an association between VS volume and craving or regulation of craving. Lack of an association between BMI and self-reported craving and regulation underscore the limitations of this image-based lab experiment, and suggest a need of future studies to examine links between real-time food consumption (e.g. an ad libitum task, or food-based imaging paradigm, i.e. Galván and McGlennen, 2012) and neural structural properties.

Learning how to manage cravings for food is fundamental for maintaining health and keeping preventable diseases (e.g. diabetes, cardiovascular disease) associated with dysregulated eating at bay. This study showed that craving for high sugar and fattening foods decreased with age, and the ability to regulate those cravings improved with age. These behaviors are supported by the maturation of frontoparietal systems implicated in cognitive control more generally. Future studies testing brain structure and volume before and after a food regulation intervention could further elucidate how brain and behavior change influence each other in the development of more adaptive eating habits. Regulation approaches such as reappraisal as used in this experiment could be one such potential intervention method as this study and others show that this technique can be easily learned and applied at all ages. With such a large proportion of the population being overweight or obese, understanding the underlying neural structures supporting the

drive to eat and to stop oneself from eating seems more important than ever.

Funding

Data sharing

Analysis code for this article is available at https://github.com/beckmart/long-appet-reg-struct. Data is available by request.

Acknowledgments

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.dcn.2019.100675.

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