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DEVELOPMENTAL NEUROPSYCHOLOGY
2016, VOL. 00, NO. 00, 1–16
http://dx.doi.org/10.1080/87565641.2016.1164172

Routledge
Taylor & Francis Group

Ventral Striatum Connectivity During Reward Anticipation in Adolescent Smokers

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ABSTRACT

Substance misusers, including adolescent smokers, often have reduced reward system activity during processing of non-drug rewards. Using a psychophysiological interaction approach, we examined functional connectivity with the ventral striatum during reward anticipation in a large (N = 206) sample of adolescent smokers. Increased smoking frequency was associated with (1) increased connectivity with regions involved in saliency and valuation, including the orbitofrontal cortex and (2) reduced connectivity between the ventral striatum and regions associated with inhibition and risk aversion, including the right inferior frontal gyrus. These results demonstrate that functional connectivity during reward processing is relevant to adolescent addiction.

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Adolescence is a period of substantial behavioral and brain changes and of heightened propensity for risk-taking. Adolescence is also a time of increased risk for impulse-control disorders, including addiction (Chambers, Taylor, & Potenza, 2014; Paus, Keshavan, & Giedd, 2008). The most common addiction in adolescence is nicotine (Young et al., 2002). Smoking is the leading cause of preventable deaths in the United States, and nearly one in five adults is a smoker (U.S. Department of Health and Human Services, 2014). Next to alcohol, cigarettes are one of the most widely available addictive substances, meaning that it is much easier for adolescents to try cigarettes than other drugs. Adolescent smoking differs widely in its frequency and regularity, but can broadly be categorized into four smoking trajectories: (1) Adolescents who start smoking at an early age and go on to become regular smokers, (2) individuals who follow the same path but initiate smoking at a later age, (3) adolescents who experiment with smoking but do not become addicted or stop smoking, and (4) non-smokers (Audrain-McGovern et al.; Chassin, Presson, Pitts, & Sherman, 2000; Mayhew, Flay, & Mott, 2000).

While the behavioral and personality differences between adolescents in different smoking trajectories are subtle and difficult to pinpoint, the differences between adolescent smokers and non-smokers are well established: Adolescent smokers show increased novelty-seeking, reduced harm avoidance, and increased choice impulsivity (Audrain-McGovern et al., 2004a, 2004b; Wills, Windle, & Cleary, 1998). However, these traits are not only characteristic of adolescent smokers compared with non-smokers, but also of adolescents compared with adults (Brändström, Sigvardsson, Nylander, & Richter, 2008; Steinberg et al., 2009). A number of neurobiological models have attributed these characteristics of the adolescent developmental period to a difference in the balance between different brain systems in adolescence. The dual-system model (e.g. Steinberg et al., 2008), the triadic model (Ernst, Pine, & Hardin, 2006) and the imbalance model (Casey, Jones, & Hare, 2008) all distinguish between the reward system and the cognitive control systems. Among the structures involved in cognitive control are the dorsolateral prefrontal cortex (dlPFC), which is one of the most important executive control regions (Alvarez & Emory, 2006), the orbitofrontal cortex (OFC), which has been attributed a role in saliency and value attribution (O'Doherty, 2004), the anterior cingulate cortex (ACC), which has been implicated in selective attention (Alvarez & Emory, 2006), and the right inferior frontal gyrus (IFG), which has been established as a central region in behavioral inhibition (Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Jacobson et al., 2003).

There are many interacting regions involved in reward processing (see Haber & Knutson, 2010). Among these regions, the ventral striatum (VS) is particularly important. The VS receives dopaminergic input from the ventral tegmental area and is connected to frontal areas such as the orbitofrontal and ventromedial cortices. The VS is not only central to processing reward-related stimuli, but also plays a key role in integrating affective and cognitive information, and in action selection and motivation (Floresco, 2015). Along with decreases in impulsive choice from adolescence to adulthood, activation in the VS during reward-related decision making decreases, and activations in prefrontal cognitive control regions have been shown to increase with age (Christakou, Brammer, & Rubia, 2011). The functional connectivity between the VS and prefrontal cortex (PFC) during reward outcomes also increases over the course of adolescence (Van Den Bos, Cohen, Kahnt, & Crone, 2012). Furthermore, ventral striatal dopamine D2 receptor availability was associated with alcohol cue-induced activation in the ACC and medial prefrontal cortex, confirming a role for dopamine in VS-medial prefrontal interactions (Heinz et al., 2004).

In adult smokers, lifetime tobacco use is associated with structural brain alterations in both the reward and cognitive control systems (Gallinat et al., 2006; Zhang et al., 2011). Furthermore, adult smokers show reduced connectivity between the striatum and ACC, associated with the severity of nicotine dependence (Hong et al., 2009). While these findings suggest a role of long-term chronic cigarette smoking in brain deficits in these systems, there is robust evidence linking the VS to adolescent impulsivity and smoking. VS hypoactivity during reward anticipation can be observed in adolescents with attention deficit hyperactivity disorder (ADHD) compared to control subjects (Scheres, Milham, Knutson, & Castellanos, 2007), and is associated with risk-

taking bias in typically developing adolescents (Schneider et al., 2012). It appears that VS activity is negatively associated with impulsivity, independent of age (Ripke et al., 2012). VS hypoactivity can be seen in dependent adult smokers compared to occasional smokers (Bühler et al., 2010), and is associated with level of nicotine use in adults (Rose, Ross, Salmeron, & Lee, 2012). Importantly, a reduction in VS activation during reward anticipation has also been observed in adolescents prenatally exposed to nicotine (Müller et al., 2013) and in adolescent smokers (Peters et al., 2011). Furthermore, Peters et al. reported that ventral striatal activity during reward anticipation was negatively correlated with smoking frequency in adolescents. These findings point toward a possible deficit in the processing of rewarding stimuli in individuals who are at risk for developing nicotine dependence.

Whereas the majority of studies to date have used measures of regional changes in Blood Oxygen Level Dependent (i.e., BOLD) activation to examine differences between substance using groups and non-users, a number of recent studies have used BOLD to evaluate differences in brain connectivity between these groups. However, the majority of these studies have focused on resting-state connectivity (Fedota & Stein, 2015). Compared with resting state measures of functional connectivity, examining differences in connectivity in relation to specific conditions, such as different reward cue types, has the potential to be more informative with regard to differences in reward processing. For instance, a study examining reward cue reactivity in smokers found greater functional connectivity between the left insula and a widespread network including the OFC, ACC, and dorsal striatum during smoking compared to food cues (Claus, Blaine, Filbey, Mayer, & Hutchison, 2013). While examining smokers' reactivity to smoking cues is a valuable tool for understanding the mechanisms of craving and relapse in addicted smokers, the way in which non-smoking rewards are processed has the potential to offer more insight into factors associated with smoking initiation and smoking trajectories in adolescents.

A task that has widely been used to examine generalized reward processing in the context of functional magnetic resonance imaging (fMRI) is the Monetary Incentive Delay (MID) task (Knutson, Westdorp, Kaiser, & Hommer, 2000). The paradigm has the distinct advantage of temporally separating anticipation and receipt of positive or negative outcomes, making it possible to examine the activation patterns associated with each separately. VS activity is observed during the anticipation of rewards in the MID (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Knutson, Fong, Bennett, Adams, & Hommer, 2003). Other regions associated with reward anticipation in this task include the dorsal striatum, cuneus, thalamus, ACC, ventromedial PFC, OFC, insula, and midbrain (Haber & Knutson, 2010; Van Leijenhorst et al., 2010).

Here, we examine the association between adolescent smoking frequency and functional connectivity in the VS during anticipation of large rewards compared to no reward in the MID task, using Psychophysiological Interaction (PPI) analysis (Friston et al., 1997). We employed a powerful machine learning procedure to examine the connectivity patterns associated with smoking. Such approaches have previously been used to investigate adolescent binge-drinking (Whelan et al., 2014) and intelligence (Jollans et al., 2015). This approach has the potential to detect relatively subtle differences, while guarding against spurious findings, using both cross-validation and random-label permutation. We included 206 adolescents from a large multisite study, with a wide spectrum of nicotine use. As our aim was to identify effects associated with smoking frequency, rather than with smoking initiation, we included only adolescents who had smoked on three or more occasions in their lifetime at the point of data collection. In line with a recent review examining resting state functional connectivity in nicotine addiction (Fedota & Stein, 2015), which concluded that disruptions in nicotine addiction appear to be focused on the salience network as well as frontal cognitive control systems, we hypothesized that frequency of smoking would be associated with reduced VS connectivity to fronto-parietal cognitive control regions (Garavan & Weierstall, 2012) and increased connectivity to regions associated with salience or valuation of stimuli, such as the anterior cingulate and orbitofrontal and insular cortices (Seeley et al., 2007).

Q3

Method

Characteristics of the IMAGEN Study

A large sample of 14-year-olds was recruited at eight recruitment sites. Adolescents completed an extensive battery of psychiatric and neuropsychological assessments, including fMRI. Details of the full study protocol and data acquisition are provided elsewhere (Schumann et al., 2010).

Participants

Participants were a subset of 206 adolescents from the multisite study (110 female). Further information on the distribution of smoking frequency is provided in Table 1, and other details about the sample are provided in Table 2.

Substance Use Questionnaire

Lifetime smoking, alcohol, and cannabis use were measured using the European School Survey Project on Alcohol and Other Drugs questionnaire (ESPAD, Hibell et al., 1997), which was administered using the computerized assessment platform Psytools. Psytools presented questionnaire items and response alternatives on a computer screen. The reliability of individual data was checked in a two-stage procedure: Before every task, adolescents were asked to report on the current testing context including questions about their attentional focus and the confidentiality of the setting. Potentially problematic testing situations were followed-up by research assistants face-to-face in a confidential setting. Exclusion criteria for substance use measures included an indication that the participant was in a hurry, somebody was watching, or an indication to have known or taken the

Table 1. Distribution of smoking frequency across the sample.

Lifetime smoking occasions		*n*
ESPAD score	ESPAD range	
2	3–5	57
3	6–9	37
4	10–19	32
5	20–39	20
6	40+	60

Table 2. Characteristics of the sample.

			Correlation with nicotine use	
	Mean	*SD*	*r*	*P*
Age	14.58	0.46	0.11	0.13
Socioeconomic Status	17.50	4.36	−0.16	0.025
Pubertal Development Status	3.66	0.70	0.13	0.065
WISC-IV Perceptual Reasoning	103.66	12.97	−0.01	0.92
WISC-IV Verbal Comprehension	107.80	13.79	−0.10	0.13
ESPAD Lifetime Alcohol use	3.21	1.63	0.26	0.0002*
ESPAD Lifetime Cannabis use	0.64	1.45	0.21	0.0029*
SURPS Anxiety Sensitivity	2.24	0.49	−0.14	0.045
SURPS Impulsivity	2.60	0.42	−0.05	0.44
SURPS Hopelessness	1.93	0.40	0.02	0.77
SURPS Sensation Seeking	2.80	0.54	−0.08	0.22
TCI-R Disorderliness	23.71	4.33	0.07	0.26
TCI-R Exploratory Excitability	33.44	4.74	0.03	0.70
TCI-R Extravagance	30.79	6.02	0.04	0.52
TCI-R Impulsivity	27.82	5.01	−0.06	0.41
TCI-R Novelty-Seeking	115.77	14.43	0.05	0.47

*$p < .003125$, p value corrected for multiple comparisons.

sham drug *Relevin*. Scores on the ESPAD are ranked as follows: 0: no lifetime use, 1: 1–2 uses, 2: 3–5 uses, 3: 6–9 uses; 4: 10–19 uses, 5: 20–39 uses, 6:40 or more uses. Participants were included if they had a score of 2 or higher on the ESPAD item measuring lifetime smoking. ESPAD scores for lifetime smoking are reported in Table 1.

Wechsler Intelligence Scale for Children

Participants completed a version of the Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003), of which we included the following subscales: Perceptual Reasoning, consisting of Block Design (arranging bi-colored blocks to duplicate a printed image) and Matrix Reasoning (a series of colored matrices are presented and the child is asked to select the consistent pattern from a range of options); and Verbal Comprehension, consisting of Similarities (two similar but different objects or concepts are presented and the child is asked to explain how they are alike or different) and Vocabulary (a picture is presented or a word is spoken aloud by the experimenter and the child is asked to provide the name of the depicted object or to define the word).

Substance Use Risk Profile Scale

The Substance Use Risk Profile Scale (SURPS; Woicik, Stewart, Pihl, & Conrod, 2009) assesses personality traits that confer risk for substance misuse and psychopathology. This scale measures four distinct and independent personality dimensions; anxiety sensitivity, hopelessness, sensation seeking, and impulsivity. The anxiety sensitivity dimension is characterized by the fear of symptoms of physical arousal. The hopelessness dimension is identified as a risk factor for the development of depression and characterized by dismal feelings. The sensation seeking dimension is characterized by the desire for intense and novel experiences. The impulsivity dimension involves difficulties in the regulation (controlling) of behavioral responses.

Temperament and Character Inventory

The novelty-seeking scale of the Temperament and Character Inventory–Revised (TCI-R; Cloninger, 1999) was administered. The Novelty-seeking scale is composed of four sub-scales. Exploratory Excitability contrasts with "stoic rigidity" and reflects sensation-seeking and novelty-seeking behaviors. Impulsiveness describes behavior on a dimension from impulsivity to reflection and captures elements of emotional reactivity, and unreflective, careless behavior. The Extravagance subscale assesses overspending behavior and poor planning and is believed to reflect a tendency to approach reward cues. Disorderliness reflects disorganized, uncontrolled, and antinormative behavior.

Puberty Development Scale

Q9 The Puberty Development Scale (PDS; Petersen, Crockett, & Richards, 1988) was used to assess the pubertal status of our adolescent sample. This scale provides an eight-item self-report measure of physical development based on the Tanner stages with separate forms for males and females. For this scale, there are five categories of pubertal status: (1) prepubertal, (2) beginning pubertal, (3) midpubertal, (4) advanced pubertal, (5) postpubertal. Participants answered questions about their growth in stature and pubic hair, as well as menarche in females and voice changes in males.

Monetary Incentive Delay Task

Participants completed a modified version of the MID task, involving small and large possible gains. On each trial, the amount of points that could be won on that trial was signaled by a cue, displayed for 4–4.5 sec. Participants could win a reward by responding as quickly as possible to a target

stimulus presented after a random time interval, by means of a button press, after which feedback was presented. The response and feedback phase lasted a total of 2 sec. The response interval was dynamically adjusted so that subjects won on 66% of all trials. Trials were separated by a 3.5–4.15 sec inter-trial interval, during which a fixation cross was presented. The cue stimuli were a circle with two lines signaling a large reward (10 points), a circle with one line signaling a small reward (2 points), and a triangle signaling that no reward could be gained. 22 trials per condition were completed, resulting in 66 total trials. Task stimuli and timings are presented in Figure 1.

fMRI Data Acquisition

Full details of the magnetic resonance imaging (MRI) acquisition protocols and quality checks have been described previously, including an extensive period of standardization across MRI scanners (Schumann et al., 2010). MRI Acquisition Scanning was performed at the eight assessment sites with a 3 T whole body MRI system made by several manufacturers (Siemens: four sites, Philips: two sites, General Electric: one site, and Bruker: one site). To ensure a comparison of MRI data acquired on these different scanners, we implemented image-acquisition techniques using a set of parameters compatible with all scanners that were held constant across sites, for example, those directly affecting image contrast or fMRI preprocessing. Standardized hardware for visual and auditory stimulus presentation (NordicNeurolabs, Bergen Norway, http://www.nordicneurolab.com) was used at all sites. BOLD functional images were acquired with a gradient-echo echoplanar imaging (EPI) sequence using a relatively short echo-time to optimize imaging of subcortical areas. For the MID, 300 volumes consisting of 40 slices were acquired for each subject. Scanning time for this task was a total of 11 minutes.

fMRI Preprocessing and Analysis

Briefly, the functional imaging processing was as follows: Time series data were first corrected for slice-timing, then corrected for movement, non-linearly warped onto MNI space using a custom EPI template, and Gaussian-smoothed at 5 mm-full width half maximum. Nuisance variables were also added to the design matrix: estimated movement was added in the form of six additional regressors (three translations, three rotations). These analysis steps were carried out in SPM8. All subsequent analyses were conducted in SPM12.

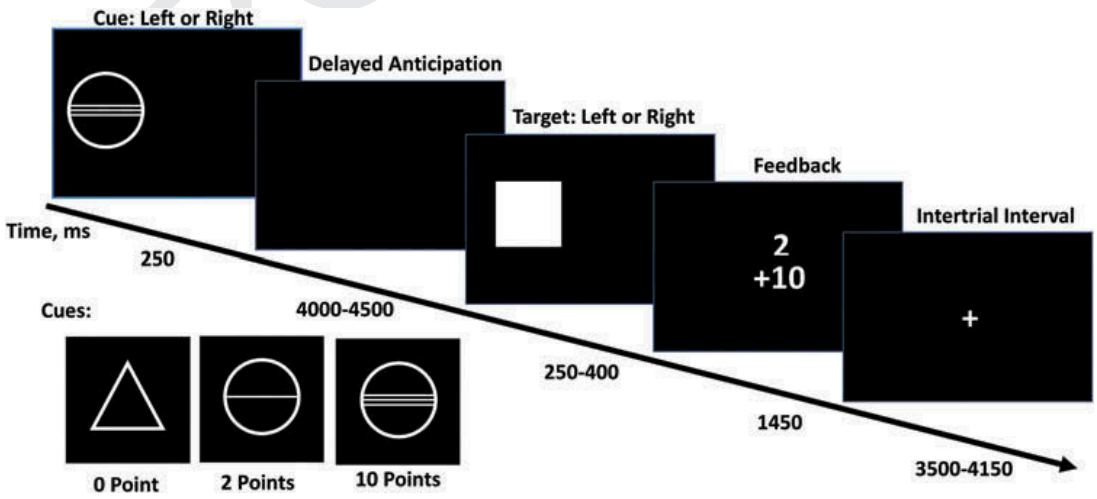

Figure 1. Stimuli and timings in the Monetary Incentive Delay (MID) task.Cues signaling the task condition (no reward, small reward, large reward) were displayed for 4–4.5 sec. The response and feedback phase lasted a total of 2 sec. Trials were separated by a 3.5–4.15 sec inter-trial interval.

Three conditions (No-win, Small-win, Big-win) in addition to individual movement parameters were specified in a general linear model. An F contrast for effects of interest was conducted after model estimation. Subsequently, BOLD signals from 3-mm radius spherical regions of interest (ROIs) in the left ventral striatum (MNI coordinates: [−12, 10, −10]) and right ventral striatum (MNI coordinates: [12, 10, −10]) were adjusted by effects of interest and extracted. These extracted signal time series were used as the physiological regressors, and the effect of condition (Big-win versus No-win) was used as the psychological regressor. The PPI term was computed using the PPI toolbox in SPM12. For further details on the PPI analysis, see Supplementary Materials.

Functional Connectivity During Reward Anticipation

A one-sample *t*-test to identify clusters in which functional connectivity for reward anticipation differed significantly from zero was conducted in SPM12. Data acquisition site, sex, and PDS were also entered into the analysis as nuisance covariates. The family-wise error ($p < .05$) was corrected for by using an uncorrected *p*-value of .001 in combination with a minimum cluster extent of 14 contiguous voxels, calculated using SPM.

Functional Connectivity Associated With Smoking Frequency

Q26 Data from 92 ROIs based on the AAL atlas (Tzourio-Mazoyer et al., 2002) and two masks for the subthalamic nuclei (x = −12, y = −10, z = −5; x = 12, y = −13, z = −5), as well as lifetime alcohol and cannabis use, data acquisition site, sex, and pubertal development status were entered into the analysis. Data were *z*-scored. The analysis procedure is shown in Figure 2. A similar approach has previously been used by Whelan et al. (2014) and Jollans et al. (2015). To assess the effect of lifetime smoking on VS connectivity, two ROI regularized multiple regression analyses for the left and right VS seed were carried out in Matlab R2014a, via the Elastic Net (Zou & Hastie, 2005). Regression with Elastic Net regularization is an example of a sparse regression method, which imposes a hybrid of both L1- and L2-norm penalties (i.e., penalties on the absolute (L1 norm) and squared values of the β weights (L2 norm)). This allows relevant but correlated coefficients to coexist in a sparse model fit, by doing automatic variable selection and continuous shrinkage simultaneously, and selects or

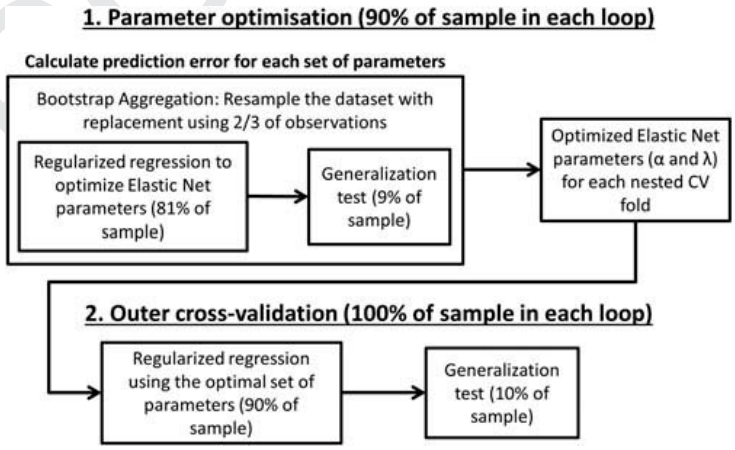

Figure 2. Machine learning analysis procedure. The machine learning analysis was carried out in two stages: (1) The optimal Elastic Net parameters for each main cross-validation (CV) fold were identified using nested CV within each main CV fold. Bootstrap aggregation was used in this step. (2) The optimal Elastic Net parameters for each main CV fold were applied to the full training set (90% of the data) to generate beta weights for all input variables. These beta weights were then used to generate outcome predictions for the remaining, untouched 10% of the dataset in each main CV fold. The goodness-of-fit was estimated using the outcome predictions for the entire dataset.

rejects groups of correlated variables. Least absolute shrinkage and selection operator (LASSO, Tibshirani, 1996) and ridge regression (Hoerl & Kennard, 1970) are special cases of the Elastic Net.

We used 10-fold nested cross-validation, in which 10 separate regression models were generated, with the beta weights for all parameters being generated on 90% of the dataset (the training set), and tested on 10% of the dataset (the test set). Within the test set, additional 10-fold cross-validation was used to identify the optimal Elastic Net parameters α and λ. Alpha represents the weight of LASSO versus ridge regularization that the Elastic Net uses, and λ is the regularization coefficient.

We additionally applied 50-fold bootstrap aggregation to introduce an additional level of stability (Breiman, 1996). That is, parameter optimization was repeated 50 times, using sampling with replacement (i.e., on average two thirds of the data in each iteration). The results from all iterations within each training fold were then averaged. In addition to bootstrap aggregation this entire analysis procedure was repeated 50 times, and the results (correlation coefficients and beta weights) were averaged across all 50 iterations of the analysis procedure. Overall, this yielded 500 sets of beta weights, from 10 cross-validation folds across 50 analysis iterations. Beta weights were averaged for each variable.

Two null models were also computed using the same method. For these, the same analysis procedure was carried out using random label permutations with the same dataset (i.e., subjects were randomly assigned to ESPAD scores). These null models yielded average beta weights of 0.018 and 0.016, and average correlation coefficients of r = −0.006 and r = −0.01. Based on the null models, the threshold for reporting ROIs was set at a minimum absolute beta weight of 0.048 this was the 95th percentile of the distribution of beta weights in the null models). The reporting thresholds for the minimum frequency with which ROIs should be included in the regression models across iterations was set at 84% (left) and 81% (right, this was the 95th percentile of the distribution of occurrence frequency across iterations in the null models).

Results

A series of Spearman's rank correlations were conducted (see Table 2). Using Bonferroni correction for multiple comparisons, lifetime smoking was significantly positively correlated with alcohol and cannabis use.

VS Connectivity during Reward Anticipation

A number of cortical and subcortical clusters showed altered functional connectivity with the VS during anticipation of a large reward versus no reward. Clusters with significantly increased or decreased functional connectivity are reported in Table 3.

Changes in VS Connectivity Associated With Lifetime Smoking

There was a significant association between lifetime smoking and both right (mean r = .27) and left (mean r = .21) VS functional connectivity. ROIs that passed the thresholds for absolute beta weights and frequency of occurrence across cross-validation folds determined using the null models are reported (see **Table 5** and Figure 3 for ROIs associated with lifetime smoking).

Discussion

A PPI analysis of a large (N = 206) sample of adolescent smokers has produced two key findings with respect to adolescent smoking frequency and functional connectivity with the VS during anticipation of rewards: (1) a positive association within the reward system; specifically, between the VS and OFC and amygdala, (2) a negative correlation between the reward system and inhibitory control and attention networks; specifically, between VS and the right IFG, inferior parietal cortex, and medial

Table 3. Clusters that showed significant changes in functional connectivity with the VS during anticipation of a large reward versus no reward.

x	y	z	k	max t	
Clusters with increased functional connectivity					
Left VS					
−6	−1	64	27	4.27	Supplemental Motor Area (L)
12	20	37	15	4.15	Middle Cingulum (R)
6	11	61	22	4.15	Supplemental Motor Area (R)
Right VS					
24	−70	−11	16	4.12	Fusiform Gyrus (R)
Clusters with decreased functional connectivity					
Left VS					
−30	−91	−11	138	7.30	Inferior Occipital Gyrus (L)
27	−94	1	105	6.24	Middle Occipital Gyrus (R)
−42	26	25	16	3.80	IFG, triangular part (L)
Right VS					
−27	−91	−11	68	6.00	Inferior Occipital Gyrus (L)
33	−88	−11	59	4.98	Inferior Occipital Gyrus (R)

Note. R = right; L = left; k = cluster extent; IFG = Inferior Frontal Gyrus.

Q22
Q23

Table 4. ROIs for which functional connectivity with the VS during anticipation of a large reward versus no reward was associated with lifetime nicotine use.

	Left VS		Right VS	
	Beta weight	% of CV folds	Beta weight	% of CV folds
Gyrus Rectus (R)	0.105	93.2	0.305	100
SFG, orbital part (R)			0.191	93.6
MFG, orbital part (L)			0.077	84.6
SFG, medial part (L)			−0.251	86.6
Olfactory gyrus (L)			−0.325	93.4
IFG, opercular part (R)			−0.176	92.4
IFG, orbital part (R)	−0.099	91.8		
Amygdala (R)			0.323	90.4
Thalamus (R)			0.150	89.6
Caudate (R)			0.076	81.2
Posterior Cingulate (L)			0.184	88.0
Posterior Cingulate (R)	0.238	88.6		
Precentral gyrus (R)			0.337	93.6
Supramarginal Gyrus (L)	0.381	84.8		
Supramarginal Gyrus (R)			−0.311	95.4
Angular Gyrus (R)			−0.138	89.6
Inferior parietal lobule (L)	−0.201	84.0		
Superior occipital gyrus (R)			−0.245	83.0
Lingual gyrus (L)			−0.100	82.6
Middle Temporal Pole (L)	−0.281	85.0		
Middle Temporal Pole (R)			−0.146	84.4
Superior Temporal Pole (R)			−0.204	96.0
Cerebellum (R)			−0.144	92.8

Note. ROI = region of interest; VS = ventral striatum; CV = cross-validation; R = right; L = left; SFG = Superior frontal gyrus; MFG = Middle frontal gyrus; IFG = Inferior Frontal Gyrus.

PFC. We also found that smoking frequency was not significantly associated with measures of impulsivity or novelty-seeking, which is in line with previous studies that were not able to distinguish between adolescent smokers in different smoking trajectories on the basis of novelty-seeking or choice impulsivity (Audrain-McGovern et al., 2004a; 2009).

Smoking frequency was associated with an increase in connectivity between the OFC and VS. The VS can indirectly modulate frontal cortical activity, by means of the thalamus. However, the ACC, medial PFC (mPFC), and OFC also provide direct input to the VS (Cohen et al., 2012; Haber & Knutson, 2010). The OFC has previously been implicated in a study comparing occasional and dependent smokers (Bühler et al., 2010). This study found that dependent smokers exhibited

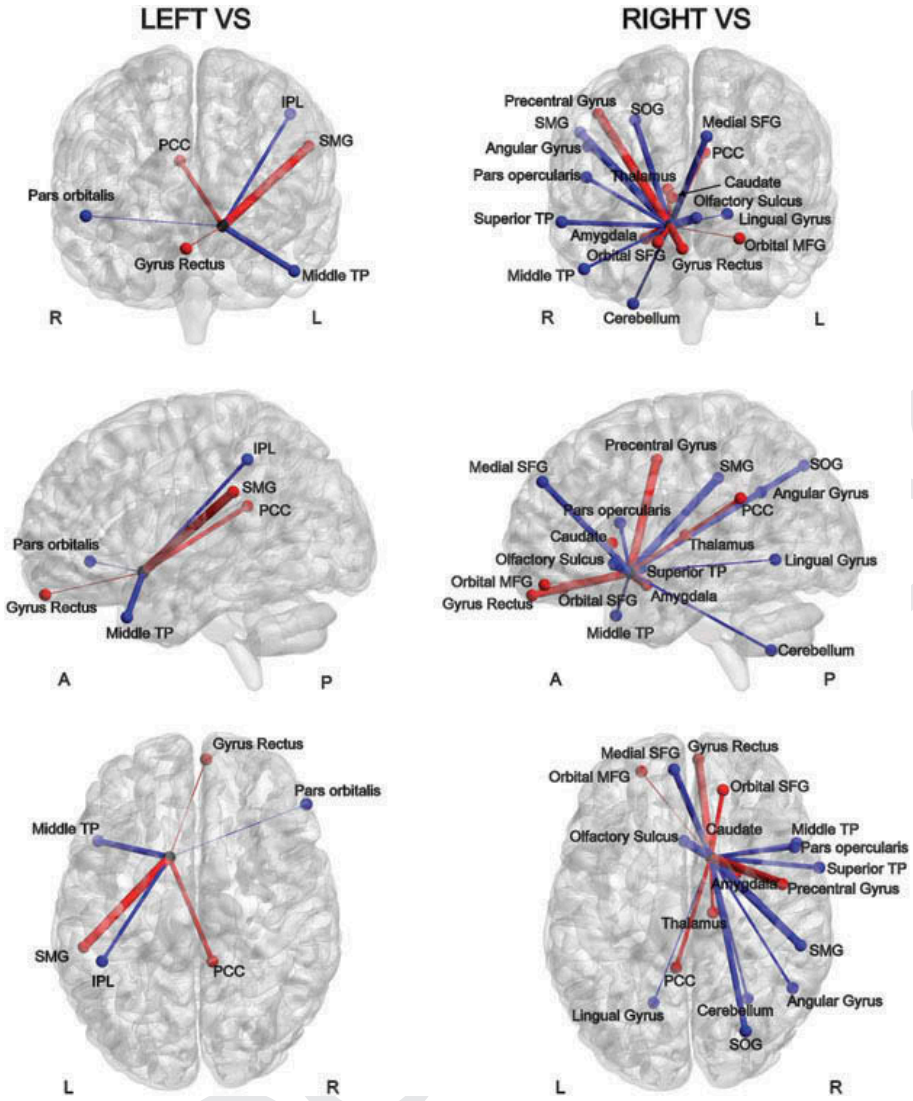

Figure 3. ROIs for which functional connectivity with the VS during anticipation of a large reward versus no reward was associated with lifetime smoking. *Note*. L = Left; R = Right; A = Anterior; P = Posterior; PCC = Posterior Cingulate; IPL = Inferior Parietal Lobule; TP = Temporal Pole; SMG = Supramarginal Gyrus; SOG = Superior Occipital Gyrus; SFG = Superior Frontal Gyrus; MFG = Middle Frontal Gyrus. Functional connectivity between the VS and nodes drawn in red was positively associated with smoking frequency. Functional connectivity between the VS and nodes drawn in blue was negatively associated with smoking frequency. This figure was generated using BrainNet Viewer (Xia, Wang, & He, 2013).

significantly less orbitofrontal activation during anticipation of monetary rewards than occasional smokers, supporting our finding of altered function of this region associated with frequency of smoking. Interestingly, the same study also reported increased activity during reward anticipation in the right medial OFC and gyrus rectus in short-term abstinent compared to non-abstinent smokers, for monetary and cigarette rewards (Bühler et al., 2010). In line with the proposed role of the OFC in attribution of saliency and valuation (O'Doherty, 2004), our finding of increased striatal connectivity with these same medial orbitofrontal regions associated with smoking frequency suggest that adolescent smoking is associated with generalized increased reward valuation; similar to the pattern demonstrated during nicotine withdrawal by Bühler and colleagues.

Thalamus–VS connectivity was also positively associated with smoking frequency. The thalamus has been highlighted as an important region in incentive processing in adolescents and adults, along with the insula (Cho et al., 2013). Cho et al. (2013) suggest that interoceptive information from the insula, and alerting signals about opportunities for incentive processing from the thalamus converge

in the nucleus accumbens (NAc), which forms part of the VS. Considering findings of increased activation in the thalamus during reward anticipation in alcoholics (Wrase et al., 2007), our finding of increased connectivity between the VS and thalamus points toward a heightened sensitivity toward salient external stimuli. We also observed increased functional connectivity between the bilateral VS and the contralateral posterior cingulate cortex (PPC), associated with smoking frequency. A general role for the PPC in directing the focus of attention internally or externally, and in determining the width or breadth of the attentional focus has been proposed (Leech & Sharp, 2014), which is consistent with its role as a central node of the default-mode network (DMN, Buckner, Andrews-Hanna, & Schacter, 2008). In monkeys PPC activity was also found to be mediated by actual and expected reward value (McCoy, Crowley, Haghighian, Dean, & Platt, 2003), and in humans the PPC has been shown to play a role in integrating motivational information and spatial attention (Mohanty, Gitelman, Small, & Mesulam, 2008). Along with the OFC, the PPC showed heightened activation during motivationally salient cues in humans (Mohanty et al., 2008), which suggests that the heightened functional connectivity between the VS and PPC may reflect a similar effect of heightened attention to highly valued and motivationally salient events as the heightened connectivity with the OFC.

In line with previous research which found that smokers show less IFG activity than non-smokers to negative emotional images (Froeliger et al., 2013), we found that functional connectivity between the VS and right IFG was negatively associated with smoking frequency. The right IFG is a central region for response inhibition (Chikazoe et al., 2007; Jacobson et al., 2003) and attentional control (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). The right IFG can also be considered part of a ventral frontoparietal attention network, which further includes the inferior parietal cortex and supramarginal gyri (Corbetta, Patel, & Shulman, 2008). This network plays a role in attentional shifting and filtering sensory input according to behavioral relevance. We also observed a strong negative association between smoking frequency and VS connectivity to regions in the mPFC. Studies of patients with lesions to the mPFC have shown that this region is involved in decision making under risk, biasing healthy individuals toward more conservative choices (Clark et al., 2008). Taken together with the finding of increased connectivity between the VS and OFC, the deficit in right IFG, inferior parietal (and superior occipital) cortex, and mPFC connectivity is consistent with the imbalance model's account of an over-active motivational system, receiving heightened input from regions central in the valuation of stimuli, and not being reigned in sufficiently by an under-active inhibitory control system and a deficit in directing attention toward behaviorally relevant stimuli.

In addition to the aforementioned ROIs, we also observed a significant association between smoking frequency and functional connectivity between the VS and the amygdala. Connectivity between the right VS and the right amygdala has been found to be associated with the relevance of stimuli (Ousdal, Reckless, Server, Andreassen, & Jensen, 2012). This is consistent with our findings of higher VS connectivity to regions associated with salience and valuation of stimuli. VS connectivity to the adjacent bilateral temporal poles on the other hand showed a strong negative association with smoking frequency. A previous study found that adult smokers' level of nicotine dependence was positively associated with activation in the temporal pole and insula during presentation of smoking compared to food cues (Claus et al., 2013). While the majority of studies examining temporal pole function have focused on social cognition and emotion processing, there is some evidence that the temporal pole could serve as a hub integrating emotional and sensory cues (Fan et al., 2014; Olson, Plotzker, & Ezzyat, 2007; Pehr et al., 2015). Furthermore, reduced grey matter volume in the temporal pole has been reported in cocaine users (Albein-Urios et al., 2013), making this region a promising target for further investigation in substance use.

While PPI analysis is a valuable tool for identifying functional differences in connectivity, it is not able to identify anatomical or structural alterations in connectivity. Conducting PPI in conjunction with tractography (e.g., Cohen, Elger, & Weber, 2008) would allow the identification of structural differences associated with functional connectivity alterations in smokers. Furthermore, PPI analyses

often suffer from a lack of power, particularly when event-related tasks are used (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). However, low power is a chronic problem in neuroimaging research (Button et al., 2013). In this study we addressed this issue by using a large sample, and a very rigorous analysis protocol. Cross-validation and bootstrapping are valuable tools for guarding against false positives (Whelan & Garavan, 2014) and identifying true, but small, effects. In addition, the random-label permutation (null model) approach that we adopted is an effective means of quantifying the validity of our results.

In conclusion, the use of a PPI analysis in conjunction with a robust machine learning approach identified differences in VS connectivity during reward anticipation associated with adolescent smoking frequency. The increased functional connectivity between the VS and OFC and PPC with increased cigarette use suggests that adolescent smoking may be associated with increased attribution of salience to reward-related stimuli. Furthermore, the finding of reduced functional connectivity between the VS and the right IFG, mPFC, and inferior parietal cortex with increased smoking indicates a deficit in inhibitory control and attentional orienting. Taken together, these findings paint a picture of increased valuation of rewards, alongside difficulties inhibiting behavior, and possibly a deficit in the integration of sensory and motivational cues in adolescent smokers. Notably, our findings extend the literature showing differences in the neural networks underpinning reward processing between adolescent smokers and non-smokers, showing that reward processing also differs between different adolescent smoking trajectories. While it is not possible to deduce whether these differences in VS connectivity preceded smoking initiation, the link between reward-related activity in the VS and adolescent impulsivity supports the conclusion that differences in VS connectivity may pose a risk for adolescent smoking. Future longitudinal studies should evaluate whether VS connectivity can be established as a predictive biomarker of substance use risk in adolescence.

Confict-of-Interest Statement

Dr. Banaschewski has served as an advisor or consultant to Bristol-Myers Squibb, Desitin Arzneimittel, Eli Lilly, Medice, Novartis, Pfizer, Shire, UCB, and Vifor Pharma; he has received conference attendance support, conference support, or speaking fees from Eli Lilly, Janssen McNeil, Medice, Novartis, Shire, and UCB; and he is involved in clinical trials conducted by Eli Lilly, Novartis, and Shire; the present work is unrelated to these relationships. Dr. Gallinat has received research funding from the German Federal Ministry of Education and Research, AstraZeneca, Eli Lilly, Janssen-Cilag, and Bristol-Myers Squibb; he has received speaking fees from AstraZeneca, Janssen-Cilag, and Bristol-Myers Squibb. Dr Barker has received honoraria from General Electric for teaching on scanner programming courses. The other authors report no biomedical financial interests or potential conflicts of interest.

Funding

Irish Research Council: GOIPG/2014/418.

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