

# Right ventromedial prefrontal cortex: a neuroanatomical correlate of impulse control in boys

Aaron D. Boes,<sup>1,2</sup> Antoine Bechara,<sup>3</sup> Daniel Tranel,<sup>4</sup> Steve W. Anderson,<sup>4</sup> Lynn Richman,<sup>5</sup> and Peg Nopoulos<sup>1</sup>

<sup>1</sup>Department of Psychiatry, <sup>2</sup>Medical Scientist Training Program, University of Iowa Carver College of Medicine, Iowa City, Iowa,

<sup>3</sup>Brain and Creativity Institute, University of Southern California, Los Angeles, California, <sup>4</sup>Division of Behavioral Neurology and Cognitive Neuroscience, Department of Neurology, University of Iowa, and <sup>5</sup>Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA

**Emerging data on the neural mechanisms of impulse control highlight brain regions involved in emotion and decision making, including the ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC) and amygdala. Variation in the development of these regions may influence one's propensity for impulsivity and, by extension, one's vulnerability to disorders involving low impulse control (e.g. substance abuse). Here we test the hypothesis that lower impulse control is associated with structural differences in these regions, particularly on the right side, in 61 normal healthy boys aged 7–17. We assessed parent- and teacher-reported behavioral ratings of impulse control (motor impulsivity and non-planning behavior) in relation to vmPFC, ACC and amygdala volume, measured using structural magnetic resonance imaging and FreeSurfer. A regression analysis showed that the right vmPFC was a significant predictor of impulse control ratings. Follow-up tests showed (i) a significant correlation between low impulse control and decreased right vmPFC volume, especially the medial sector of the vmPFC and (ii) significantly lower right vmPFC volume in a subgroup of 20 impulsive boys relative to 20 non-impulsive boys. These results are consistent with the notion that right vmPFC provides a neuroanatomical correlate of the normal variance in impulse control observed in boys.**

**Keywords:** impulsive; FreeSurfer; brain development; structural MRI; attention deficit hyperactivity disorder; externalizing

## INTRODUCTION

Some people plan extensively and maintain a high level of restraint, whereas others routinely act on the spur of the moment, with little regard to consequences. These differences form a core dimension of human personality and behavior that is fairly heritable, emerges early in the course of development and persists across developmental stages (McKay and Halperin, 2001; Kochanska and Knaack, 2003). Impulsiveness can impact several domains of child development, being negatively associated with educational achievement in children (Blair and Razza, 2007) and positively associated with future substance use (Tarter *et al.*, 2003; Nigg *et al.*, 2006) and criminal activity (Babinski *et al.*, 1999).

There appears to be a behavioral continuum of impulsiveness in the population that spans from physiological to pathological levels for disorders such as attention deficit–hyperactivity disorder (ADHD) (Haslam *et al.*,

2006; Frazier *et al.*, 2007). In addition to ADHD, impulsivity is a hallmark feature of substance abuse and antisocial personality disorder, among others (Moeller *et al.*, 2001).

There is heightened interest in understanding the factors that contribute to individual differences in impulsivity based on its important role in behavior. A major hurdle in this endeavor is clarifying the term *impulsivity*. It is often used broadly in the literature to encompass distinct functions such as non-planning behavior and cognitive impulsivity that likely have different neural substrates (Bechara, 2005) and may contribute differentially to disorders involving poor impulse control. Here we study motor impulsivity (e.g. restless, cannot sit still; hyperactive, always on the go) and non-planning behavior (e.g. acts without stopping to think, wants things right away, blurts things out), which combine to form a measure of impulse control (also see 'Materials and methods' section).

It is increasingly recognized that brain regions involved in emotion and decision making influence impulse control. The ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC) and amygdala, in particular, are believed to provide critical neural substrates for impulse control (Bechara, 2005). Accumulated evidence from lesion studies shows that damage to these regions is often associated with deficits in emotion, decision making and impulse control (Bechara *et al.*, 2000; Berlin *et al.*, 2004; Bechara and Van Der Linden, 2005; Anderson *et al.*, 2006). Also noteworthy,

Received 11 February 2008; Accepted 17 September 2008

Advance Access publication 19 October 2008

We thank Chadi Calarge, MD, for helpful suggestions with an earlier version of the manuscript, Amy Conrad, PhD, for her assistance in data collection and Eric Axelson and Greg Harris for technical support. The anatomical accuracy of the tracing protocol was confirmed by Martin Cassell, PhD, a neuroanatomist from the University of Iowa Department of Anatomy and Cell Biology with expertise in amygdala anatomy. This study was supported by the National Institute of Dental and Craniofacial Research (1 R01 DE01 14399 01 A1, partial to P.N.); National Institute on Drug Abuse (NIDA R01 DA022549 to D.T.); National Institutes of Health; National Center for Research Resources; General Clinical Research Centers Program Grant (RR00059).

Correspondence should be addressed to Aaron Boes, University of Iowa Hospitals and Clinics, W278 GH, 200 Hawkins Drive, Iowa City, IA 52242. E-mail: aaron-boes@uiowa.edu

there is preliminary evidence suggesting that right-sided structures may be preferentially involved in males. For instance, unilateral damage to the right-sided vmPFC and amygdala in males is associated with more severe emotional and behavioral impairment in comparison to similar lesions on the left side [Tranel, D. and Bechara, A. (Submitted); Tranel *et al.*, 2002, 2005].

Converging research on the neural underpinnings of disorders characterized by poor impulse control also highlight the vmPFC–ACC–amygdala circuit. Functional and structural differences in this circuit are associated with an array of disorders in which poor impulse control is commonly attributed, including substance abuse (Bechara *et al.*, 2001; Hill *et al.*, 2001, 2006; Franklin *et al.*, 2002), antisocial behavior (Damasio, 2000; Davidson *et al.*, 2000; Blair *et al.*, 2001; Sterzer *et al.*, 2005; Stadler *et al.*, 2007; Boes *et al.*, 2008a) and ADHD (Shaw *et al.*, 2007). This line of research, too, often shows preferential involvement of the right hemisphere (Hill *et al.*, 2001; Sterzer *et al.*, 2005; Shaw *et al.*, 2007; Stadler *et al.*, 2007; Boes *et al.*, 2008a). An issue of considerable importance in understanding the biological contribution to these aforementioned disorders is whether vulnerability is influenced by developmental variation in this emotion processing circuit. A few studies have addressed this topic of vulnerability. There are several genetic polymorphisms that impact impulsivity (Kreek *et al.*, 2005) and emerging evidence that these genetic variations correspond to differences in the structure and function of the vmPFC–ACC–amygdala circuit (Pezawas *et al.*, 2005; Meyer-Lindenberg *et al.*, 2006; Buckholz *et al.*, 2007; Rao *et al.*, 2007; Shaw *et al.*, 2007).

The tantalizing implication from this body of work is that heritable biological markers of vulnerability to impulsive disorders may lie in regional structural and functional differences in the brain in the absence of pathology. To date, though, no studies have addressed whether behavioral measures of impulse control correspond to differences in the structure of this emotion processing circuit in normal healthy young people.

The current study is the second of a two-part analysis of the neuroanatomical correlates of externalizing behavior (Boes *et al.*, 2008b). Here we investigate the relationship between behavioral ratings of impulse control (specifically motor impulsivity and non-planning behavior) and volume of the vmPFC, ACC and amygdala. We hypothesized that in a large sample of boys, aged 7–17, without evidence of psychopathology, ratings of impulse control would be directly related to the volumetric measures. Only boys were included in the analysis based on the higher prevalence of impulse control problems in boys and to eliminate the confounding influence that sex differences in brain structure may introduce. We predict that boys with lower impulse control have decreased volume of these regions, especially right-sided structures based on previous reports suggesting right hemispheric dominance for emotion and behavior regulation in males [Tranel, D. and Bechara, A. (Submitted); Tranel *et al.*, 2005; Boes *et al.*, 2008b].

## MATERIALS AND METHODS

### Participants

A total of 61 healthy boys, aged 7–17, were recruited from the community using local advertisements. These participants served as a comparison group for another study on brain structure and function in children with cleft lip and palate (Nopoulos *et al.*, 2007). A phone screening interview was performed to exclude participants with any medical or neurological disease that required significant medical intervention. Additional exclusion criteria included any current or past diagnosis of a psychiatric disorder or learning disorder, as reported by parents. The protocol was approved by the University of Iowa Human Subjects Institutional Review Board, and written informed consent was obtained for all participants prior to participation.

### Demographics

Demographic data included age, parental socioeconomic status (SES), IQ and handedness. SES was determined using a modified Hollingshead scale of 1 to 5, with a lower number corresponding to higher social class (Hollingshead, 1975). IQ was estimated using the full-scale Wechsler Intelligence Scale for Children, fourth edition (Wechsler, 2003). Handedness was determined using the Physical and Neurological Evaluation of Subtle Signs (Denckla, 1985).

### Behavioral measure

The Pediatric Behavior Scale, short version (PBS) is a tool for assessing emotional and behavioral problems. It was derived from the Pediatric Behavior Scale (Lindgren and Koeppel, 1987), a measure with similar items as the Child Behavior Checklist (Achenbach and Edelbrock, 1983). For each participant, a parent and a teacher were asked to rate problems on a 4-point Likert scale (0–3), with a lower score indicating fewer problems. For the current analysis, only questions related to non-planning and motor impulsivity were included, which together comprised the impulse control measure. Individual questions included (i) impulsive, acts without stopping to think; (ii) cannot stand waiting, wants things right away; (iii) interrupts, talks out of turn or blurts things out; (iv) hyperactive, always on the go, (v) squirms or fidgets; and (vi) restless, cannot sit still. The parent and teacher response rate for the PBS was 100 and 90%, respectively. As a means of data reduction, the PBS ratings from the parent and teacher were summed to preserve information from both parent and teacher and maximize the range of behavioral variance. The parent's rating was doubled for subjects without teacher-reported ratings ( $n = 6$ ). The intra-class correlation between parent and teacher ratings was estimated ( $r = 0.46$ ,  $P = 0.01$ ) using a two-way analysis of variance model.

The PBS scales were derived from factor analysis with varimax rotation from a sample of 600 children aged 6–12. The scales were obtained from a four-factor solution, with all eigenvalues greater than 1. All the items on this scale do

not cross-load to any significant degree ( $<0.30$ ) with other PBS scales. The reliability of the PBS impulse control scale was established using a longer version of the PBS, which estimated the internal consistency coefficient at 0.95 for the category including impulse control questions (Lindgren and Koepl, 1987). The criterion for inclusion of items in the short PBS version is that items load on highly similar factors in the normal structure of the child behavior checklist in both sexes across multiple age categories. The scale used in this study has a raw mean score of 3.82 from the normative sample (parent rating only). The PBS has been shown to be valuable in identifying symptoms of ADHD in a sample of children with cleft (Richman *et al.*, 2004), as well as identifying attention deficits in a normal sample (Johnson *et al.*, 1999).

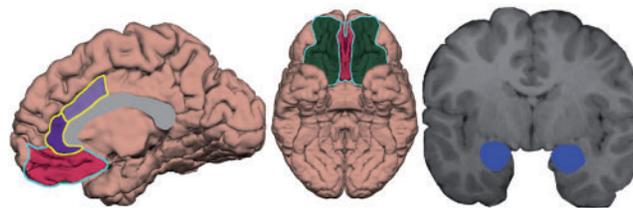
The PBS was also used as a proxy to a formal evaluation for ADHD to exclude participants who were likely to meet Diagnostic and Statistical Manual IV ADHD criteria. Exclusionary criteria were met if both parent and teacher rated the participant above the 90th percentile in two of the three ADHD-like scales (hyperactive/motor impulsivity, impulsive/non-planning and inattentive), as described as a method of ADHD diagnosis by Richman *et al.* (2004). The 90th percentile was determined using normative data from 6- to 12-year-old boys ( $n=300$ ). No participants met the exclusionary criteria.

### Magnetic resonance imaging acquisition

Magnetic resonance imaging (MRI) scans were obtained using a 1.5 Tesla General Electric SIGNA System (GE Medical Systems, Milwaukee, WI). Three-dimensional T1-weighted images were acquired in the coronal plane using a spoiled grass sequence with the following parameters: 1.5 mm coronal slices,  $40^\circ$  flip angle, 24 ms repetition time (TR), 5 ms echo time (TE), two numbers of excitations (NEX), 26 cm field of view (FOV) and a  $256 \times 192$  matrix. The proton density (PD) and T2-weighted images were acquired with the following parameters: 3.0 mm coronal slices, 36 ms TE (for PD) or 96 ms TE (for T2), 3000 ms TR, 1 NEX, 26 cm FOV,  $256 \times 192$  matrix and an echo train length = 1.

### Image processing

MRI data were processed using BRAINS2 (Brain Research: Analysis of Images, Networks, and Systems), our locally developed software, described elsewhere (Magnotta *et al.*, 2002). T1-weighted images were spatially normalized and resampled to  $1.015625 \text{ mm}^3$  voxels, and the anterior-posterior axis of the brain was realigned parallel to the anterior commissure-posterior commissure line. The inter-hemispheric fissure was aligned by selecting points along the fissure in the coronal and axial views. T2- and PD-weighted images were aligned to the spatially normalized T1-weighted image (Woods *et al.*, 1992) to allow the use of a multimodal discriminant classifier. The tissue-classified image was used to generate a triangle-based isosurface using a threshold of 130, representing prototypical gray



**Fig. 1** This figure shows a medial (left) and ventral (right) view of the cerebral cortex demonstrating the regions of interest for the current study. The ventromedial prefrontal cortex is outlined in light blue and contains the mOFC in red and IOFC in dark green, according to the FreeSurfer terminology (also see description in 'Materials and methods' section). The anterior cingulate cortex is outlined in yellow and is composed of the rostral anterior cingulate (dark purple) and caudal anterior cingulate (light purple). The corpus callosum (in gray) was generated manually and included to illustrate a relevant landmark. The amygdala is shown in blue on a coronal image.

matter (Chemerinski *et al.*, 2002). An initial polygonalization of cortical surface was done (Wyvill, 1986). A retiling algorithm (Turk, 1992) was used to reduce the image to a more manageable size, to approximately 100 000 triangles per hemisphere from the initial 300 000 to 500 000. This triangulated image was used as the basis for our calculations of amygdala volume.

The T1 acquisition was processed using FreeSurfer (<http://www.martinos.org/freesurfer>), an automated parcellation software program (Desikan *et al.*, 2006). The output of interest was total cerebral cortex gray matter volume and volume of the predefined regions of interest (ROIs), the vmPFC and ACC. The anatomical accuracy of each FreeSurfer ROI was visually inspected, and those with unacceptable parcellation were excluded from all analyses (two right ACC and five left ACC). Common reason for exclusion was only the outer portion of a double cingulate was labeled or the corpus callosum-ACC border was poorly defined.

### Regions of interest

Figure 1 displays the anatomical ROIs for the current study, derived from the standard FreeSurfer atlas. The vmPFC is composed of two regions defined by FreeSurfer, the medial orbitofrontal cortex (mOFC) and lateral orbitofrontal cortex (IOFC). The mOFC is composed of the ventral sector of the medial prefrontal cortex and the orbitofrontal cortex medial to the olfactory sulcus (i.e. straight gyrus). The IOFC is flanked by the olfactory sulcus medially and the lateral orbital sulcus laterally. FreeSurfer parcellation divides the ACC into a rostral and caudal division (rACC and cACC, respectively), which were summed to form ACC volume. Details of FreeSurfer parcellation, including reliability, validity and anatomical boundaries, are described in detail elsewhere (Desikan *et al.*, 2006). The intraclass correlation coefficient (ICC) describing the correlation of automated and manual parcellation methods for all ROIs in the cerebral cortex was 0.835, with ICC values of individual ROIs as follows: L rACC = 0.811; R rACC = 0.835; L cACC = 0.768;

R cACC = 0.809; L mOFC = 0.834; R mOFC = 0.907; L IOFC = 0.865; R IOFC = 0.814 (Desikan *et al.*, 2006).

Amygdala volume was generated by manual tracing in the BRAINS2 environment. T1, T2 and PD images were loaded, and three orthogonal views were simultaneously viewed. Tracing was done in the coronal plane, and the rater was blind to subject identity. Prior to tracing the current data, A.D.B. established intrarater reliability on a separate set of 20 amygdalae (intraclass *R* coefficient of 0.95 for right and 0.92 for left). The tracing protocol is similar to methods developed by Schumann and Amaral (Schumann *et al.*, 2004), though the image was aligned using different methods (described above).

**Statistical analysis.** All analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL). The relationship of externalizing behavior ratings to multivariate predictors was assessed with hierarchical multiple regression. Step 1 of the regression included demographic variables (age, IQ, SES) and total gray matter volume of the cerebral cortex. In Step 2, right- and left-sided ROIs were entered in the regression model separately to evaluate whether they differ in predictive value. We hypothesized that right-sided ROIs would significantly predict impulse control but did not predict a significant interaction effect for right and left ROIs, as decreased volume was predicted for both hemispheres.

Significant structural findings in the regression model were followed up with Spearman correlation coefficients to further investigate the nature of the structure–function relationship. Subregions within the cortical ROIs that significantly correlated with impulse control ratings were included in the correlation test to assess whether one subregion preferentially contributed to significant findings. We performed two additional analyses, aimed at assessing the specificity of our correlation test and ruling out alternative explanations. We chose a specific region of the cortex that we hypothesized would have no relationship to our behavioral measure, the occipital lobe, and correlated its gray matter volume with impulse control ratings. Next, we replaced the impulse

control ratings with the physical health PBS ratings and repeated the correlation test, predicting a non-significant correlation.

ROI volumes that significantly correlated with impulse control ratings were compared in boys in the upper and lower tercile of the impulse control scale using analysis of covariance (ANCOVA) (general linear model, univariate analysis of variance). Twenty participants at each end of the impulse control behavioral scale form the terciles. The a priori decision to divide the group into terciles instead of quartiles or by the median score was intended to select subjects who differ substantially at the behavioral level while also including a sufficient number of subjects to obtain statistical power. The purpose of this analysis was to determine whether volumetric differences driving significant correlations reached statistical significance in comparing participants at each end of the behavioral scale. Also, demographic variables were compared among these groups.

## RESULTS

### Descriptive findings

Table 1 reports the demographic, behavioral and structural data for all participants. IQ scores are consistent with the demographics of Iowa (Lindgren *et al.*, 1985) though may also be artificially high from a selection bias introduced through recruitment via advertisements. PBS impulse control ratings from the parent compare favorably to the normative data (derived from parent-only ratings) at 3.29 and 3.82, respectively. The PBS behavioral data were positively skewed. Table 1 also divides the descriptive data into a younger ( $\leq 12$ ) and older ( $\geq 13$ ) age group to evaluate the influence of age on these variables.

### Regression

Results of the hierarchical multiple regression analyses are summarized in Table 2. Right and left ROIs were included in separate models. In both models, Step 1 included

**Table 1** Descriptive data: demographic, behavioral and structural

	Measure	Boys ( $n = 61$ )	Younger ( $\leq 12$ ) ( $n = 45$ )	Older ( $\geq 13$ ) ( $n = 16$ )	<i>P</i>
Age	Range	7.75–17.92	7.75–12.92	14.08–17.92	–
	Mean (s.d.)	12.08 (2.71)	10.69 (1.46)	15.97 (1.08)	<0.0005
IQ	Mean (s.d.)	112 (16)	115 (17)	103 (9)	0.01
SES	Mean (s.d.)	2.29 (0.57)	2.24 (0.59)	2.43 (0.51)	0.24
Handedness		53 RH, 7 LH, 1 A	40 RH, 5 LH	13 RH, 2 LH, 1A	–
Impulse control	Range	0–26	0–26	0–17	–
	Mean (s.d.)	5.39 (5.13)	5.66	4.62	0.49
R VMPC Vol	Mean (s.d.)	14.86 (1.33)	14.89 (1.25)	14.79 (1.57)	0.79
L VMPC Vol	Mean (s.d.)	15.28 (1.60)	15.12 (1.53)	15.75 (1.77)	0.17
R ACC Vol	Mean (s.d.)	3.93 (0.60)	3.93 (0.63)	3.96 (0.52)	0.87
L ACC Vol	Mean (s.d.)	3.97 (0.73)	3.83 (0.74)	4.29 (0.60)	0.03
R Amygdala Vol	Mean (s.d.)	1.31 (0.18)	1.27 (0.17)	1.40 (0.20)	0.01
L Amygdala Vol	Mean (s.d.)	1.29 (0.18)	1.27 (0.17)	1.36 (0.18)	0.08

Volumetric measures are in cubic centimeters.

A, ambidextrous; L, left; LH, left handed; R, right; RH, right handed; Vol, volume.

**Table 2** Predictors of impulse control

	Right-sided ROIs		Left-sided ROIs	
	$\beta$	Sig	$\beta$	Sig
<i>Step 1<sup>a</sup></i>				
SES	-0.18	0.20	-0.18	0.20
Age	-0.15	0.30	-0.15	0.31
IQ	-0.13	0.38	-0.13	0.39
Total cortex volume	-0.06	0.66	-0.42	0.67
<i>Step 2<sup>b</sup></i>				
vmPFC	-0.46	0.006	-0.25	0.23
ACC	-0.23	0.08	-0.18	0.28
Amygdala	0.01	0.91	0.00	0.99

<sup>a</sup>Right side:  $R^2$  change = 0.05,  $F$  change = 0.733, Sig. = 0.57; Left side:  $R^2$  change = 0.05,  $F$  change = 0.71, Sig. = 0.58; <sup>b</sup>Right side:  $R^2$  change = 0.17,  $F$  change = 3.66, Sig. = 0.01; Left side:  $R^2$  change = 0.05,  $F$  change = 0.96, Sig. = 0.41;  $\beta$  = Standardized beta coefficient.

**Table 3** Correlation of impulse control and right-sided ROI volume

ROI	Impulse control
vmPFC	-0.31 (0.01) [-0.33 (0.009)]
mOFC	-0.34 (0.006) [-0.34 (0.006)]
lOFC	-0.16 (0.21) [-0.14 (0.26)]

R, right; Bracketed values are for Spearman partial correlation with total cortex volume as a covariate.

demographic data (IQ, SES, age) and total gray matter volume of the cerebral cortex. Step 2 included volumetric measures of the vmPFC, ACC and amygdala. Impulse control ratings were rank ordered to correct a positive skew. For the right-sided ROIs, the change in  $R^2$  was statistically significant for Step 2 ( $P=0.01$ ), with an effect size estimated at 0.127 using Cohen's  $f^2$ . Individually, only the right vmPFC contributed significantly ( $P=0.006$ ), with a trend toward significance in the right ACC ( $P=0.08$ ). As a result, subsequent analyses were limited to the right vmPFC.

**Correlation**

Table 3 reports Spearman correlation results of impulse control ratings and volumetric measures of the right-sided vmPFC, as well as subregions within the vmPFC. There was a statistically significant negative (inverse) correlation of impulse control ratings and volume of the right vmPFC, such that increased impulsiveness corresponded to low volume. The subregion analysis demonstrated that this correlative relationship was significant for the medial sector of the vmPFC and not the lateral sector. Also displayed in Table 3 in brackets are the results of a Spearman partial correlation with total cortex volume as a covariate. Correlation tests assessing the specificity of these findings were all non-significant. Spearman correlation coefficients of occipital lobe gray volume and impulse control were not

**Table 4** Comparison of upper and lower tertiles

	Measure	Lower tertile	Upper tertile	$F$	Sig
		( $n=20$ )	( $n=20$ )		
Age	Range	9.08–17.00	7.75–17.00		
	Mean (s.d.)	12.09 (2.48)	11.42 (2.71)		0.42
IQ	Mean (s.d.)	114 (16)	114 (20)		0.99
	Mean (s.d.)	2.36 (0.58)	2.03 (0.46)		0.05
SES	Mean (s.d.)	2.36 (0.58)	2.03 (0.46)		0.05
Handedness		17 RH, 3 LH	18 RH, 2 LH		
Impulsivity rating	Range	0–2	7–26		
	Mean (s.d.)	1.25 (0.85)	10.95 (5.29)		0.000
Total cortex volume (cc)	Mean volume (s.d.)	510 (37)	501 (30)		0.45
	Adjusted mean volume (s.e.m.) <sup>a</sup>	15.18 (1.20)	14.46 (1.37)	5.20	0.02
R vmPFC (cc)	Adjusted mean volume (s.e.m.) <sup>a</sup>	6.03 (0.73)	5.48 (0.69)	6.94	0.01

cc, cubic centimeters; L, left; LH, left handed; R, right; RH, right handed; <sup>a</sup>ANCOVA tests covary for SES.

significant in the right or left hemisphere ( $r=-0.03$ ,  $P=0.78$  for each). The PBS physical health rating was used as a control behavioral measure and did not correlate significantly with volume of the right vmPFC ( $r=-0.07$ ,  $P=0.58$ ). A limitation of this control behavioral measure is lower variance relative to the impulse control measure, with mean and standard deviation values of 1.45 (1.81) vs 5.39 (5.13).

**Extreme group comparison**

Table 4 displays independent  $t$ -tests of quantitative descriptive data comparing boys in the upper and lower tertile of impulse control ratings ( $n=20$ /group). Significant differences were noted for SES and behavioral ratings of impulse control, the latter was expected based on the classification approach. The  $t$ -score difference between the upper (raw score 10.95) and the lower (raw score 1.25) tertile is  $\sim 1.8$  s.d. An ANCOVA covarying for SES evaluated whether the vmPFC and mOFC (the subregion that correlated most with impulsiveness) differed significantly between groups. Boys in the upper tertile (impulsive boys) had lower volume of the right vmPFC ( $F=5.20$ ,  $P=0.02$ ) and right mOFC ( $F=6.94$ ,  $P=0.01$ ).

**DISCUSSION**

These results support the hypothesis that the right vmPFC acts as a neuroanatomical correlate of impulse control in normal healthy boys. Overall, the significant results were as follows: (i) a regression analysis revealed that as a group the right-sided ROIs (vmPFC, ACC and amygdala) significantly predicted impulse control ratings, with the vmPFC as the only independently significant predictor within this group; (ii) a follow-up correlation analysis revealed a statistically significant negative correlation of impulse control and volume of the right vmPFC, which was more robust in the medial sector; and (iii) ANCOVA showed that the volume

of the right vmPFC and the medial sector of the vmPFC region (i.e. the mOFC) was significantly smaller in impulsive boys (i.e. the upper tercile relative to the lower). There is some support for specificity in the relationship of vmPFC volume and impulse control. Another PBS rating scale, physical health, did not correlate with vmPFC volume in the current analysis, nor did aggression and defiance after regressing out impulse control, as reported previously (Boes *et al.*, 2008b).

There was a trend toward significance for low right ACC volume predicting decreased impulse control ( $P=0.08$ ). In contrast, a relationship of amygdala volume and impulse control was not identified. This was unexpected and may be related to low variance in amygdala volume relative to the cortical regions. Decreased amygdala volume has been observed in association with high risk for disorders of impulse control, including substance abuse (Hill *et al.*, 2001). Perhaps assigning risk via family history instead of or in addition to behavior would have been revealing, though the current design did not allow this. We now turn our attention to a discussion of how variations in the development of the right vmPFC region may impact impulse control.

One interpretation of the vmPFC finding is that impulse control improves with age, and older boys have larger vmPFCs. This seems unlikely. A *post hoc* analysis shows that the difference in impulse control ratings in older ( $\geq 13$  years) vs younger ( $<12$  years) boys in this sample is non-significant ( $P=0.83$ ). In general, impulse control is believed to improve with age along with development of the prefrontal cortex (Casey *et al.*, 2005; Galvan *et al.*, 2007). For the current sample, it is possible that parents and teachers rated these behaviors relative to the boys' age-matched peers, though the PBS instructions did not explicitly instruct this. With regard to vmPFC development, we have previously shown that while overall cerebral cortex gray matter volume decreases over the age span of 7–17, there is a sex-specific non-dynamic trajectory of volumetric change in the vmPFC in boys, presumably because maturational pruning occurs later in adolescence and early adulthood (Boes, 2008).

Over a decade's worth of research has supported the critical role of the vmPFC in guiding advantageous behavior. A major function of this cortical region may be tagging the emotional salience of stimuli and experiences and using this information to assign value to possible behavioral outcomes. Consistent with this idea, vmPFC damage attenuates the autonomic responses normally seen in passive anticipation of a potentially aversive event (Bechara *et al.*, 1999). The vmPFC figures prominently in a neurocognitive theory for impulse control (Bechara, 2005; Bechara and Van Der Linden, 2005). This theory proposes that two separate and interacting sets of neural systems vie for behavior. An impulsive system involves the amygdala and signals the immediate prospects of pain or pleasure, while a reflective system requiring the vmPFC takes into account the long-term prospects of a given action. These systems compete for behavior

via neural mechanisms aligned with the principles of natural selection (Bechara and Damasio, 2005). Impulsive behavior, or a 'myopia for the future' (Bechara *et al.*, 1994) may result from an imbalance of these systems favoring amygdala > vmPFC.

Complimentary processes that engage the vmPFC may also contribute to impulse control. For instance, the vmPFC may be necessary for empathy and affective theory of mind (Shamay-Tsoory *et al.*, 2003, 2005; Amodio and Frith, 2006). Because many impulsive acts are selfish in nature, they may stem from difficulty predicting the harmful effects of one's behavior on others. Extinction of classically conditioned associations in the face of changing contingencies may also facilitate impulse control. This capacity is believed to depend on vmPFC projections to the amygdala (Phelps *et al.*, 2004), and the effectiveness of extinction learning has been directly correlated to vmPFC thickness (Milad *et al.*, 2005). Inhibiting emotional responses via projections to the amygdala and other emotional effector structures may also be relevant, as impulse control is often compromised in the throes of a strong emotion (e.g. crimes of passion).

Another aim of the current analysis was to assess whether laterality impacts the relationship of impulse control and brain morphology. Our findings support this notion, as only the right vmPFC significantly predicted impulse control. This is interesting in light of recent findings hinting at the possibility of right-sided dominance in the neural substrates of emotion and behavior regulation in males. As noted previously, unilateral damage to the right vmPFC results in more severe emotional and behavioral impairment in men relative to comparable left-sided lesions. Moreover, another analysis of the participants in the current study revealed a significant inverse relationship of right ACC volume and aggression and defiance, with impulse control as a covariate (Boes *et al.*, 2008b). The laterality of significant findings in the current analysis fits in a very intriguing manner the emerging evidence of the aforementioned studies. These preliminary findings warrant that future studies of this emotion processing circuit take into account the possibility of lateralized findings.

A formal clinical evaluation was not performed to exclude the possibility that participants from the community could have undiagnosed psychopathology that may influence the results (e.g. anxiety, substance abuse, ADHD). As a result, the conclusions from this normal healthy sample must be qualified by mentioning this omission. Undiagnosed ADHD is a particular concern because the behaviors assessed here overlap with hyperactive and impulsive ADHD symptoms. The PBS scale was used as a proxy to assess whether the participants met ADHD criteria (described in 'Materials and methods'). Considering that no participants met the ADHD exclusion criteria we believe it unlikely that the significant findings here are driven solely by boys with undiagnosed ADHD. Rather, our results may suggest continuity in

the neuroanatomical correlates of impulse control that spans normal and pathological groups, as occurs for behavioral symptoms. While several studies have shown reduced right prefrontal cortex volume or reduced dorsolateral PFC volume in association with ADHD (for review see Seidman *et al.*, 2005), few have looked specifically at the vmPFC. In studies that use an unbiased whole-brain analysis, the results thus far are mixed, with some showing structural change in the vmPFC (Carmona, 2005; Carmona *et al.*, 2005; Shaw *et al.*, 2006b, 2007) and others that do not (Overmeyer *et al.*, 2001; Sowell *et al.*, 2003). It may be that inattentive symptoms are associated with differences in the dorsolateral PFC, while impulse control is more closely related to structure and function of the vmPFC and affective neural systems. Further studies are needed to address this issue empirically.

Limitations of the study are the following. (i) The behavioral measure assesses only a few major symptoms of motor impulsivity and non-planning behavior. The addition of laboratory tasks measuring these behaviors may have further clarified the behavioral profile. (ii) The study is cross-sectional and spans a wide age range. The results do not address whether the developmental trajectory of the ROIs differs with impulsive behavior in a dynamic way (see Shaw *et al.*, 2006a). (iii) Bechara (2005) hypothesized that the anterior vmPFC may be more critical for decision making (possibly corresponding to non-planning impulsivity), when contingencies are projected in the distant future or are of uncertain probability. In contrast, deficits in the posterior vmPFC (including ACC and basal forebrain) may result in impulsivity that occurs here and now, in response to tangible incentives or high probability events (corresponding to motor impulsivity). The current results support this hypothesis, but non-planning and motor impulsivity are combined in the impulse control measure, and the anatomical parcellation scheme does not distinguish between the anterior and posterior vmPFC (a discrete anatomical boundary has not been proposed). Therefore, these more refined hypotheses were not tested. Future research must be directed at parceling out how the vmPFC implements various functions underlying the subcategories within the broader construct of impulsivity (Patton *et al.*, 1995; Evenden, 1999; Whiteside and Lynam, 2001; Winstanley *et al.*, 2006). Ultimately, several independent systems interacting to influence different aspects of impulsive behavior may be discovered.

Despite these limitations, the current study contributes to the recent upsurge of research on the biological underpinnings of impulse control. Most intriguingly, recent studies have begun to discover genes that likely impact impulse control and corresponding differences in the structure and function of an emotion processing brain circuit. The emerging picture is a set of genes (many involved in monoaminergic transmission) that alters brain development in a way that increases one's proclivity for impulsiveness, and by extension, one's vulnerability for certain disorders that are

notoriously difficult to manage (e.g. substance abuse, ADHD, antisocial disorders). A host of questions arise from the possibility of identifying neural 'endophenotypes' for impulse control. How does one's environment interact with susceptibility genes to impact brain development in this circuit? Can therapeutic intervention be optimized if tailored to one's unique genetic vulnerability? Will biological markers of vulnerability someday be utilized to initiate preventative efforts for high-risk individuals? Clearly, there is much work to be done. These important topics have some experimental traction, though, with convergent data from several labs implicating variations in vmPFC as a possible biological marker of vulnerability for disorders of impulse control.

### Conflict of interest

None declared.

### REFERENCES

- Achenbach, T.M., Edelbrock, C. (1983). *Manual for the Child Behavior Checklist and Revised Child Behavior Profile*. Burlington, VT: University of Vermont.
- Amodio, D.M., Frith, C.D. (2006). Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews: Neuroscience*, 7, 268–77.
- Anderson, S., Barrash, J., Bechara, A., Tranel, D. (2006). Impairments of emotion and real-world complex behavior following childhood- or adult-onset damage to ventromedial prefrontal cortex. *Journal of the International Neuropsychological Society*, 12, 224–35.
- Babinski, L.M., Hartsough, C.S., Lambert, N.M. (1999). Childhood conduct problems, hyperactivity-impulsivity, and inattention as predictors of adult criminal activity. *Journal of Child Psychology & Psychiatry & Allied Disciplines*, 40, 347–55.
- Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nature Neuroscience*, 8, 1458–63.
- Bechara, A., Damasio, A.R. (2005). The somatic marker hypothesis: a neural theory of economic decision. *Games and Economic Behavior*, 52, 336–72.
- Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50, 7–15.
- Bechara, A., Damasio, H., Damasio, A.R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex*, 10, 295–307.
- Bechara, A., Damasio, H., Damasio, A.R., Lee, G.P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *Journal of Neuroscience*, 19, 5473–81.
- Bechara, A., Dolan, S., Denburg, N., Hinds, A., Anderson, S.W., Nathan, P.E. (2001). Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia*, 39, 376–89.
- Bechara, A., Van Der Linden, M. (2005). Decision-making and impulse control after frontal lobe injuries. *Current Opinion in Neurology*, 18, 734–9.
- Berlin, H.A., Rolls, E.T., Kischka, U. (2004). Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. *Brain*, 127, 1108–26.
- Blair, C., Razza, R.P. (2007). Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in kindergarten. *Child Development*, 78, 647–63.
- Blair, R.J., Colledge, E., Mitchell, D.G. (2001). Somatic markers and response reversal: is there orbitofrontal cortex dysfunction in boys with psychopathic tendencies? *Journal of Abnormal Child Psychology*, 29, 499–511.
- Boes, A.D. (2008). *Neuroanatomical Correlates of Externalizing Behavior*. Iowa City: University of Iowa, pp. 107.

- Boes, A.D., McCormick, L.M., Coryell, W.H., Nopoulos, P. (2008a). Rostral anterior cingulate cortex volume correlates with depressed mood in normal healthy children. *Biological Psychiatry*, 63, 391–7.
- Boes, A.D., Tranel, D., Anderson, S.W., Nopoulos, P. (2008b). Right anterior cingulate: a neuroanatomical correlate of aggression and defiance in boys. *Behavioral Neuroscience*, 122, 677–84.
- Buckholtz, J.W., Callicott, J.H., Kolachana, B., et al. (2007). Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality. *Molecular Psychiatry*, 13, 313–24.
- Carmona, S., Vilarroya, O., Bielsa, A., et al. (2005). Global and regional gray matter reductions in ADHD: a voxel-based morphometric study. *Neuroscience Letters*, 389, 88–93.
- Casey, B.J., Galvan, A., Hare, T.A. (2005). Changes in cerebral functional organization during cognitive development. *Current Opinion in Neurobiology*, 15, 239–44.
- Chemerinski, E., Nopoulos, P.C., Crespo-Facorro, B., Andreasen, N.C., Magnotta, V. (2002). Morphology of the ventral frontal cortex in schizophrenia: relationship with social dysfunction. *Biological Psychiatry*, 52, 1–8.
- Damasio, A.R. (2000). A neural basis for sociopathy. *Archives of General Psychiatry*, 57, 128–9.
- Davidson, R.J., Putnam, K.M., Larson, C.L. (2000). Dysfunction in the neural circuitry of emotion regulation—a possible prelude to violence [see comment]. *Science*, 289, 591–4.
- Denckla, M. (1985). Revised neurological examination for subtle signs. *Psychopharmacology Bulletin*, 21, 773–800.
- Desikan, R.S., Segonne, F., Fischl, B., et al. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*, 31, 968–80.
- Evenden, J.L. (1999). Varieties of impulsivity. *Psychopharmacology (Berl)*, 146, 348–61.
- Franklin, T.R., Acton, P.D., Maldjian, J.A., et al. (2002). Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. *Biological Psychiatry*, 51, 134–42.
- Frazier, T.W., Youngstrom, E.A., Naugle, R.I. (2007). The latent structure of attention-deficit/hyperactivity disorder in a clinic-referred sample. *Neuropsychology*, 21, 45–64.
- Galvan, A., Hare, T., Voss, H., Glover, G., Casey, B.J. (2007). Risk-taking and the adolescent brain: who is at risk? *Developmental Science*, 10, F8–14.
- Haslam, N., Williams, B., Prior, M., Haslam, R., Graetz, B., Sawyer, M. (2006). The latent structure of attention-deficit/hyperactivity disorder: a taxometric analysis. *Australian and New Zealand Journal of Psychiatry*, 40, 639–47.
- Hill, S., Kostelnik, B., Wang, S.H., et al. (2006). Affective circuitry in unaffected adolescent/young adult offspring from multiplex alcohol dependence families: structural and functional MRI studies. *Neuropsychopharmacology*, 31, S204.
- Hill, S.Y., De Bellis, M.D., Keshavan, M.S., et al. (2001). Right amygdala volume in adolescent and young adult offspring from families at high risk for developing alcoholism. *Biological Psychiatry*, 49, 894–905.
- Hollingshead, A. (1975). *Four Factor Index of Social Skills*. New Haven, CT: Yale.
- Johnson, B., Altmaier, E., Richman, L. (1999). Attention deficits and reading disabilities: are immediate memory deficits additive? *Developmental Neuropsychology*, 15, 213–26.
- Kochanska, G., Knaack, A. (2003). Effortful control as a personality characteristic of young children: antecedents, correlates, and consequences. *Journal of Personality*, 71, 1087–112.
- Kreek, M.J., Nielsen, D.A., Butelman, E.R., LaForge, K.S. (2005). Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nature Neuroscience*, 8, 1450–7.
- Lindgren, S., De Renzi, E., Richman, L.C. (1985). Cross-national comparisons of developmental dyslexia in Italy and the United States. *Child Development*, 56, 1404–17.
- Lindgren, S., Koepl, G. (1987). *Assessing Child Behavior Problems in a Medical Setting: Development of the Pediatric Behavior Scale*. Prinz, RJ, editor. Greenwich, CT: JAI Press.
- Magnotta, V.A., Harris, G., Andreasen, N.C., O’Leary, D.S., Yuh, W.T., Heckel, D. (2002). Structural MR image processing using the BRAINS2 toolbox. *Computerized Medical Imaging and Graphics*, 26, 251–64.
- McKay, K.E., Halperin, J.M. (2001). ADHD, aggression, and antisocial behavior across the lifespan. Interactions with neurochemical and cognitive function. *Annals of the New York Academy of Sciences*, 931, 84–96.
- Meyer-Lindenberg, A., Buckholtz, J.W., Kolachana, B., et al. (2006). Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proceedings of the National Academy of Sciences of the United States of America*, 103, 6269–74.
- Milad, M.R., Quinn, B.T., Pitman, R.K., Orr, S.P., Fischl, B., Rauch, S.L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 10706–11.
- Moeller, F.G., Barratt, E.S., Dougherty, D.M., Schmitz, J.M., Swann, A.C. (2001). Psychiatric aspects of impulsivity. *American Journal of Psychiatry*, 158, 1783–93.
- Nigg, J.T., Wong, M.M., Martel, M.M., et al. (2006). Poor response inhibition as a predictor of problem drinking and illicit drug use in adolescents at risk for alcoholism and other substance use disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, 45, 468–75.
- Nopoulos, P., Langbehn, D.R., Canady, J., Magnotta, V., Richman, L. (2007). Abnormal brain structure in children with isolated clefts of the lip or palate. *Archives of Pediatrics & Adolescent Medicine*, 161, 753–8.
- Overmeyer, S., Bullmore, E.T., Suckling, J., et al. (2001). Distributed grey and white matter deficits in hyperkinetic disorder: MRI evidence for anatomical abnormality in an attentional network. *Psychological Medicine*, 31, 1425–35.
- Patton, J.H., Stanford, M.S., Barratt, E.S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, 51, 768–74.
- Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., et al. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nature Neuroscience*, 8, 828–34.
- Phelps, E.A., Delgado, M.R., Nearing, K.I., LeDoux, J.E. (2004). Extinction learning in humans: role of the amygdala and vmPFC. *Neuron*, 43, 897–905.
- Rao, H., Gillihan, S.J., Wang, J., et al. (2007). Genetic variation in serotonin transporter alters resting brain function in healthy individuals. *Biological Psychiatry*, 62, 600–6.
- Richman, L.C., Ryan, S., Wilgenbusch, T., Millard, T. (2004). Overdiagnosis and medication for attention-deficit hyperactivity disorder in children with cleft: diagnostic examination and follow-up. *Cleft Palate–Craniofacial Journal*, 41, 351–4.
- Schumann, C.M., Hamstra, J., Goodlin-Jones, B.L., et al. (2004). The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. *Journal of Neuroscience*, 24, 6392–401.
- Seidman, L.J., Valera, E.M., Makris, N. (2005). Structural brain imaging of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 57, 1263–72.
- Shamay-Tsoory, S.G., Tomer, R., Berger, B.D., Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. *Journal of Cognitive Neuroscience*, 15, 324–37.
- Shamay-Tsoory, S.G., Tomer, R., Berger, B.D., Goldsher, D., Aharon-Peretz, J. (2005). Impaired “affective theory of mind” is associated with right ventromedial prefrontal damage. *Cognitive and Behavioral Neurology*, 18, 55–67.
- Shaw, P., Gornick, M., Lerch, J., et al. (2007). Polymorphisms of the dopamine d4 receptor, clinical outcome, and cortical structure in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 64, 921–31.
- Shaw, P., Greenstein, D., Lerch, J., et al. (2006a). Intellectual ability and cortical development in children and adolescents. *Nature*, 440, 676–9.
- Shaw, P., Lerch, J., Greenstein, D., et al. (2006b). Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, 63, 540–9.

- Sowell, E.R., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A. W., Peterson, B.S. (2003). Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Lancet*, 362, 1699–707.
- Stadler, C., Sterzer, P., Schmeck, K., Krebs, A., Kleinschmidt, A., Poustka, F. (2007). Reduced anterior cingulate activation in aggressive children and adolescents during affective stimulation: association with temperament traits. *Journal of Psychiatric Research*, 41, 410–7.
- Sterzer, P., Stadler, C., Krebs, A., Kleinschmidt, A., Poustka, F. (2005). Abnormal neural responses to emotional visual stimuli in adolescents with conduct disorder. *Biological Psychiatry*, 57, 7–15.
- Tarter, R.E., Kirisci, L., Mezzich, A., et al. (2003). Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *American Journal of Psychiatry*, 160, 1078–85.
- Tranel, D., Bechara, A., Denburg, N.L. (2002). Asymmetric functional roles of right and left ventromedial prefrontal cortices in social conduct, decision-making, and emotional processing. *Cortex*, 38, 589–612.
- Tranel, D., Damasio, H., Denburg, N.L., Bechara, A. (2005). Does gender play a role in functional asymmetry of ventromedial prefrontal cortex? *Brain*, 128, 2872–81.
- Turk, G. (1992). Re-tiling polygonal surfaces. *Computer Graphics*, 26, 620–633.
- Wechsler, D. (2003). *Wechsler Intelligence Scale for Children—Fourth Edition*. San Antonio, TX: Psychological Corporation.
- Whiteside, S.P., Lynam, D.R. (2001). The five factor model and impulsivity: using a structural model of personality to understand impulsivity. *Personality & Individual Differences*, 30, 669–89.
- Winstanley, C.A., Eagle, D.M., Robbins, T.W. (2006). Behavioral models of impulsivity in relation to ADHD: translation between clinical and pre-clinical studies. *Clinical Psychological Review*, 26, 379–95.
- Woods, R.P., Cherry, S.R., Mazziotta, J.C. (1992). Rapid automated algorithm for aligning and reslicing PET images. *Journal of Computer Assisted Tomography*, 16, 620–33.
- Wyvill, G.M., McPheeters, C., Wyvill, B. (1986). Data structures for soft objects. *The Visual Computer*, 2, 227–34.