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Genetic contribution to the phenotypic correlation between trait impulsivity and resting-state functional connectivity of the amygdala and its subregions

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ABSTRACT

Trait impulsivity, a predisposition to respond to stimuli without regard for the potentially negative consequences, contributes to many maladaptive behaviors. Studies have shown that both genetic factors and interregional functional interactions underlie trait impulsivity. However, whether common genes contribute to both trait impulsivity and its neural basis is still unknown. This study investigated the phenotypic correlations between trait impulsivity and the resting-state functional connectivity (rsFC) of the amygdala as well as its subregions and the genetic contribution to the phenotypic correlations. By recruiting a sample of 292 twins in late adolescence and young adulthood, we found that trait impulsivity was positively correlated with the rsFC between the left full amygdala and the right dorsolateral prefrontal cortex (DLPFC). Further analyses on the subregions of the amygdala showed that trait impulsivity was positively correlated with the rsFCs between the left basolateral (BL) amygdala and both the right DLPFC and the right inferior frontal gyrus and with the rsFCs between the right superficial (SF) amygdala and both the dorsal anterior cingulate cortex and right anterior insula. Bivariate genetic modelling analyses found genetic overlaps between trait impulsivity and the rsFC of the left full amygdala or the left BL amygdala with the right DLPFC. The proportions of phenotypic associations accounted for by overlapping genes were 82% and 60%, respectively. These results provide evidence for the genetic overlap between trait impulsivity and the intrinsic brain functional connectivity centered at the amygdala and especially at its BL subregion.

1. Introduction

Trait impulsivity is defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others" (Moeller et al., 2001). Higher impulsivity is linked with many psychiatric disorders, including addictions (Carmona-Perera et al., 2018), attention deficit/hyperactivity disorder (Jepsen et al., 2018), borderline personality disorder (Sher et al., 2018), and mood disorders (Peluso et al., 2007). Trait impulsivity also has an advantage in situations in which a rapid response is necessary and takes advantage of unexpected opportunities (Bevilacqua and Goldman, 2013). Given the maladaptive and adaptive characteristics of trait impulsivity, understanding the biological basis of the individual differences in trait impulsivity is vital.

Behavioral genetic studies have repeatedly found that trait impulsivity is under genetic control. Three preliminary twin studies consistently found that 45% of the variance in trait impulsivity was accounted for by genetic factors (Congdon and Canli, 2008). A recent meta-analysis of twin, family and adoption studies supported this earlier finding by finding equal proportions of variance due to genetic (0.5) and non-shared environmental (0.5) influences and no shared environmental effects explaining individual differences in impulsivity regardless of the method of assessment (laboratory task vs. questionnaires). The relative contributions of genetic effects and unique environmental effects were also found to be important throughout development from childhood to adulthood (Bezdjian et al., 2011) and to have strong genetic continuity

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from mid to late adolescence (Niv et al., 2012).

Neuroimaging studies examining the neural basis of trait impulsivity involving tasks such as emotion processing (Brown et al., 2006), reward anticipation (Kerr et al., 2015), and response inhibition (Brown et al., 2006; Goya-Maldonado et al., 2010; Horn et al., 2003) have shown that trait impulsivity is related to task-evoked brain activities in both the subcortical regions and prefrontal cortices (PFC), especially in the amygdala, anterior cingulate cortex (ACC), and ventral PFC. These findings suggest that functional interactions between subcortical regions, such as the amygdala, and prefrontal cortices, may underlie trait impulsivity. Using resting-state functional connectivity (rsFC), a powerful tool that builds the bridge between intrinsic brain activity during rest and behavioral trait or cognitive activity (Cole et al., 2014; Di Martino et al., 2009; Raichle, 2010; Smith et al., 2009), investigators have provided evidence that trait impulsivity is linked to the rsFC between the amygdala and prefrontal cortices, including the ventral ACC (Kerr et al., 2015), the right dorsolateral prefrontal cortex (DLPFC) and orbital frontal cortex (Ko et al., 2015). However, not much is known about the neural correlates of trait impulsivity in late adolescence and early adulthood. The rsFC continues to change across the lifespan (Zuo et al., 2017), even during this time period (Petrican et al., 2017; Richmond et al., 2016; Stevens, 2016; Zhang et al., 2016). Therefore, the neural correlates of trait impulsivity remain to be determined in late adolescence and early adulthood, which is a critical development period for both the healthy population and patients with psychiatric disorders (Havighurst, 1972; Kessler et al., 2005).

The importance of the functional interaction centered at the amygdala in trait impulsivity is further exemplified in models that account for impulse control in addiction or risk-taking behavior in adolescence and youths, in which trait impulsivity is an important risk factor (Romer, 2010). In a model of an imbalance between separate but interacting neural systems, which was proposed to account for impulse control and decision making in addiction (Bechara, 2005), the amygdala is considered a critical region in an impulsive system that signals the affective/emotional attributes of the immediate prospect, and interacts with the PFC system (including the lateral PFC and ACC as well as ventromedial PFC), a reflective system, that is in charge of signaling the affective/emotional attributes of the future prospect. Amygdala-related circuits are also highlighted in a triadic model accounting for risk-taking behavior in adolescence as a center of emotion/avoidance systems (Ernst, 2014), which cooperate with approach systems centered on striatal function and control systems centered on the PFC proposed in the dual systems model and its variants (Casey et al., 2008; Luciana and Collins, 2012; Shulman et al., 2016; Steinberg, 2008).

Accumulating evidence supports that genetic factors contribute to the inter-individual differences in the structure and function of the amygdala (Budisavljevic et al., 2016; Chen, 2014; Renteria et al., 2014; Roshchupkin et al., 2016; Swagerman et al., 2014; Wen et al., 2016; Wolfensberger et al., 2008). Recently, similar to other measurements of functional connectivity during rest (Adhikari et al., 2018; Colclough et al., 2017; Glahn et al., 2010; Yang et al., 2016); individual differences in the rsFC of the amygdala have been demonstrated to be controlled by genetic factors, while the rsFC of the amygdala is also influenced by environmental factors (for a review see (Richmond et al., 2016)). Specifically, the variance in the rsFC between the amygdala and the orbital frontal cortex is explained by genetic factors, but the variance in the rsFC between the amygdala and the ventral ACC has been explained by a shared environment in childhood (Achterberg et al., 2018). It should be noted that the amygdala is not a single unit but consists of multiple and functionally distinct subregions (Amunts et al., 2005; Ball et al., 2007). One study took this functional heterogeneity of the amygdala subregions into consideration and found that individual differences in the strength of rsFC between the central nucleus of the amygdala and the bed nucleus of the stria terminalis are significantly heritable in rhesus monkey (Fox et al., 2018).

In brief, the experimental findings and theoretical models suggest the importance of amygdala-centered circuits in trait impulsivity, especially the functional interaction between the amygdala and PFC. Genetic factors separately contribute to trait impulsivity and the rsFC of the amygdala. However, whether common genetic factors contribute to trait impulsivity and amygdala-centered circuits is still unknown. The current study investigated this question by using a sample of late-adolescent and young adult twins. We used rsFC to build the connectivity between the amygdala and other regions in the brain. First, we conducted seed-based functional connectivity analysis by taking the left or right amygdala as a seed. Then, we linked the rsFC with trait impulsivity measured using the youth version of the Barratt Impulsive Scale-11 (youth BIS-11) (Niv et al., 2012; Patton et al., 1995). Finally, we explored the genetic and/or environmental overlaps between trait impulsivity and the rsFCs centered at the amygdala. Based on the role of the functional interaction between the amygdala and PFC in trait impulsivity as we introduced earlier, we speculate that the neural correlates of trait impulsivity and genetic/environment contributions to the phenotypic correlations may be located in the rsFC between the PFC and amygdala.

Furthermore, to explore which subregion of the amygdala plays a major role in the phenotypic correlation and the genetic and/or environmental overlaps with trait impulsivity, we applied a common tripartite solution of the amygdala in human (the basolateral (BL), centromedial (CM) and superficial (SF) amygdala) (Amunts et al., 2005) to conduct seed-based functional connectivity analyses by taking each subregion of the amygdala as a seed and then repeating the above-mentioned phenotypic correlation and genetic correlation analyses. There are two reasons driving us to further analyse the amygdala subregions. First, recent studies on the rsFC of the human amygdala support the importance of examining the subregions of the amygdala separately rather than treating the amygdala as a unitary structure in order to better understand the functional specialization of the amygdala by showing distinct coactivation and connectivity patterns of each subregion (Bzdok et al., 2013; Kerestes et al., 2017; Roy et al., 2009). Specifically, the BL amygdala, composed of the lateral, basolateral, basomedial, and basoventral nuclei, is primarily engaged in significance detection and associative learning processes through afferent inputs from cortical and subcortical regions, including the thalamus, hippocampus, and prefrontal cortex (Bzdok et al., 2013; LeDoux et al., 1990; Phelps and LeDoux, 2005); the CM amygdala, composed of the central and medial nuclei, is associated with mediating attentional, vegetative and motor responses through connectivity with the brainstem and cortical and striatal regions (Bzdok et al., 2013; Davis, 1997; LeDoux, 2003); the SF, adjacent to the BL, is involved in olfactory and affective processes through bilateral connections with the limbic regions (Bzdok et al., 2013; Heimer and Van Hoesen, 2006; Price, 2003). Second, our previous study suggested that not all amygdala subregions showed the same functional connectivity pattern associated with one specific trait (Wu et al., 2016). Because the amygdala subregions show distinct connectivity patterns with other regions, including the PFC, during rest, although they have convergent connectivity with the right ventrolateral PFC (Kerestes et al., 2017; Roy et al., 2009), we speculate that the neural correlates of trait impulsivity in the amygdala-PFC connectivity may be regionally dependent and thus that the genetic/environment contributions to the phenotypic correlations may also be regionally dependent.

2. Materials and methods

2.1. Participants

The participants were from the Beijing Twins Brain-Behavior Association Project, in which a total of 153 same-sex healthy twin pairs (81 monozygotic (MZ), 72 dizygotic (DZ)) in late adolescent and young adulthood participated in this study. The participants were recruited through the Beijing Twin Study at the Institute of Psychology, Chinese Academy of Sciences (Chen et al., 2013). Their ages ranged from 16 to 28 years (mean = 21.2 years, SD = 2.8; 48.4% were women). After

excluding the participants with severe head motion (see the below), neuroimaging data from 146 twin pairs were included in the analyses. The demographic information of participants was showed in Table 1. The zygosity of the twins was determined using DNA analyses (Chen et al., 2010).

None of the participants had a current/history of physical/psychiatric diagnoses, neurological or metabolic illnesses, or head injuries based on their self-reports. This study was approved by the Institutional Review Board of the Institute of Psychology of the Chinese Academy of Sciences. Written informed consent was obtained from all the participants, and each of them received a financial reward after the experiment in appreciation for their time and participation.

2.2. Measurement of trait impulsivity

We used a youth version of the BIS-11 (youth BIS-11) to measure trait impulsivity (Niv et al., 2012). Similar to the adult version, the youth BIS-11 is a 30-item Likert-type questionnaire divided into three subscales reflecting the attention, motor and non-planning aspects of impulsivity. Because the total score is often recommended to measure trait impulsivity (Cross et al., 2011), especially in youth (Paloyelis et al., 2010), we used the youth BIS-11 total score as the measurement of trait impulsivity in this study. The total score showed good reliability (Cronbach's $\alpha = 0.74$), suggesting that this score can be used to measure trait impulsivity. Higher scores reflect higher trait impulsivity levels.

2.3. Image acquisition and fMRI protocols

MRI scans were acquired using a GE 3.0 T MRI scanner at the Magnetic Resonance Imaging Research Center, Institute of Psychology, Chinese Academy of Sciences. For each participant, structural and functional MRI scans were obtained. Structural MRI scans were acquired using a magnetization-prepared rapid acquisition gradient echo sequence with the following parameters: repetition time (TR) = 6.89 m s, echo time (TE) = 2.98 m s, flip angle = 8°, acquisition matrix = 256 × 256, and field of view (FOV) = 256 mm × 256 mm; 176 sagittal slices, with a thickness of 1 mm, were obtained. Functional images were acquired using an echo planar imaging (EPI) sequence with the following parameters: TR = 2000 m s, TE = 30 m s, flip angle = 90°, acquisition matrix = 64 × 64, and FOV = 220 mm × 220 mm; 35 axial slices, with a thickness of 3.5 mm and a gap of 0.5 mm, were scanned for each participant. During the scan, participants were instructed not to focus their thoughts on anything in particular and to keep their eyes closed. The duration of the resting-state fMRI was 8 min.[2]

2.4. fMRI data preprocessing

Conventional functional imaging preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF 4.3, http://rfmri.org/dpabi) (Yan et al., 2016), which is based on Statistical Parametric Mapping (SPM12) (http://www.fil.ion.ucl.ac.uk/spm) and the Resting-State fMRI Data Analysis Toolkit (REST 1.8, http://www.restfmri.net) (Song et al., 2011). The preprocessing steps included the removal of the first 10 vol, corrections for slice timing and spatial registration, segmentation of the T1 map to generate the grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) regions (Ashburner and Friston, 2005), nuisance variable regression, spatial normalization with 2-mm cubic voxels, spatial smoothing with a 4 mm FWHM kernel and temporal band-pass (0.01–0.1 Hz) filtering. The nuisance variables included 24 motion parameters (6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items), 5 principal components from the individual segmented CSF and WM regions (Behzadi et al., 2007), and linear and quadratic trends (Yan et al., 2013b). The volume-based framewise displacement (FD) was used to quantify head motion (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012). To further reduce the influences of motion-related artifacts on rsFC, we employed volume-based scrubbing regression by including scrubbing regressors into the multiple linear regression (Yan et al., 2013a). The time points with a threshold of FD > 0.2 mm as well as 1 back and 2 forward frames were identified and then modeled as a separate regressor in the regression model of the realigned resting fMRI data. We excluded 7 participants and their co-twins (Table 1) who had less than 120 "good" volumes of data (Yan et al., 2013a). No participants had a mean FD above 3 standard deviations beyond the mean value of the whole sample.

2.5. Resting-state functional connectivity of amygdala and its subregions

The procedures used here closely follow those used in (Bzdok et al., 2013; Kerestes et al., 2017). To facilitate comparisons across papers, with the editor's permission we largely reproduce their description here, noting any differences specific to the present study. Seed-based resting-state functional connectivity (rsFC) analyses were conducted for the left and right full amygdala and for each subregion of the amygdala, including the basolateral (BL: left 237 voxels, right 215 voxels), centromedial (CM: left 43 voxels, right 11 voxels) and superficial (SF: left 36 voxels, right 48 voxels) amygdala in both hemispheres (Fig. 1). The seeds for the amygdala subregions were derived from a histological definition of the amygdala using the SPM Anatomy toolbox (Eickhoff et al., 2005, 2006). The three subdivisions of the amygdala have been previously cytoarchitectonically mapped in ten human postmortem brains, 3D reconstructed and mapped to standard Montreal Neurological Institute (MNI) space (Amunts et al., 2005). The resulting maximum probability map (MPM) represents the most likely cytoarchitectonical area at each voxel of the reference space and hence provides a discrete representation of microanatomically defined areas in standard space. These amygdala subregions have also been identified by connectivity-based parcellation and task coactivation of the human amygdala, showing spatial continuity and localization consistent with the cytoarchitectonically defined nuclei (Bzdok et al., 2013; Kerestes et al., 2017). We used the MPM for each of the three subdivisions of the amygdala as our seed for rsFC analysis, which were resampled with a voxel size of $2 \times 2 \times 2\ mm^3$. The left and right full amygdala were the unions of the left and right three subregions, respectively.

Then, we computed Pearson's correlation between the mean time series of each seed region and the time series of each voxel from a GM mask. The GM mask was generated by including the voxels in which all subjects' GM were averaged and the GM value was larger than 0.2. Then, to ensure that the GM voxels had EPI signals, the GM mask was multiplied by a group EPI mask generated by DPABI 3.0 (http://rfmri.org/dpabi) (Yan et al., 2016), in which the voxels appeared in more than 90% of subjects. After a Fisher r-to-Z translation, the Z-score map of rsFC for each seed region was generated. To build the phenotypic correlation between trait impulsivity and rsFC, we conducted a multiple regression analysis to

Table 1
Demographic information of participants.

		Included Twins (N = 292)	Excluded twins (N = 14)	χ^2/t	p
Age (Mean ± SD)		21.30 ± 2.83	19.71 ± 2.33	2.07	0.04
Gender	Male	152	6	0.45	0.50
	Female	140	8		
Race	Han	264	14	1.47	0.69
	Man	16	0		
	Hui	10	0		
	Chaoxian	2	0		
Zygosity	MZ	158	4	3.50	0.06
	DZ	134	10		
BIS total score (Mean ± SD)		74.44 ± 12.36	78.86 ± 10.65	−0.72	0.47

[2] These data are available upon direct request for use by qualified researchers.

identify the regions whose rsFC showed a significant correlation with the youth BIS-11 total score on the group level. To avoid inflated effect sizes and SEs, we controlled for family structure as in Vainik et al. (2018) and Kim (2016). Specifically, to exclude the influence of the non-independence of observations within twin pairs, hierarchical linear modelling (HLM) (Raudenbush and Bryk, 2002) was used to present phenotypic associations between the impulsivity trait and the value of the rsFCs. We fitted a voxel-wise linear mixed model with a random family effect to account for the twin correlations using the lmer function (lme4 package in R) (Bates et al., 2015). It should be noted that the residual error of each voxel's rsFC value after regressing out age, gender and head motion was entered into the HLM analysis. Correction for multiple comparisons was conducted with AFNI (version 17.2.07) using the following parameters: voxels in the GM mask were 187599, Gaussian filter width (FWHM) was estimated by 3dFWHMx, individual voxel threshold was $p < 0.001$ and cluster level threshold was $p < 0.05$ when performing 3dClustSim correction. Thus, the statistical significance threshold for each voxel-wise HLM analysis was a corrected $p < 0.05$. Furthermore, considering that the HLM analysis was repeated twice for the full amygdala, we used Bonferroni correction for multiple comparisons of the number of analyses (i.e., corrected $p < 0.05/2 = 0.025$ for the full amygdala) (Worsley, 2001). To explore the region-dependence of the phenotypic correlations, we conducted the same analysis for each subregion of the amygdala. Then, we extracted the mean rsFC within each cluster showing significant correlations with trait impulsivity (corrected $p < 0.05$) for further genetic modelling analyses.

2.6. Genetic analyses

Twin analyses were conducted using OpenMx (Boker et al., 2011; Neale et al., 2003) on R (version 3.1.2, http://www.R-project.org/) (Venables and Smith, 2013). A classic twin study evaluates the proportion of phenotypic variation attributable to genetic variation among individuals (A, additive effect) and what proportions are due to shared/common (C, e.g., parents' educational level, family's social-economic status) and non-shared/ unique environmental factors (E, unique experience inside or outside the family and measurement error) (Plomin et al., 2008). This decomposition is based on the following assumptions: monozygotic twins are 100% genetically identical, whereas dizygotic twins are, on average, 50% identical for genetic effects; 100% of the common environment is shared by all siblings, and 0% of the unique variance is shared between siblings. A univariate model is able to estimate the A, C and E influences on the variance of one phenotype (such as trait impulsivity). One limitation of the twin design relies on the assumption that the genetic and environmental influences on a trait are simple additive, which ignores the possible gene-environmental interaction. However, twins studies can still inform us about the relative importance of genes and environment on one specific trait and on the correlation between two traits (Guo, 2005).

In addition to establishing univariate heritability, one can also conduct heritability analysis on the covariance between two traits. A correlated factors model was fitted to the data to decompose the phenotypic correlation between trait impulsivity and the rsFC of the amygdala subregions into A, C, and E components (Loehlin, 1996) (Fig. 2). Here, r_g represents the extent of overlap between the genetic factors influencing trait impulsivity and those influencing the mean rsFC, r_c indicates the extent of the overlap of the shared environmental factors, and r_e indicates the extent of the overlap of the non-shared environmental factors as well as measurement errors.

Initially, a full bivariate correlated-factors ACE model was fitted using maximum likelihood estimation. Then, the submodels (AE, CE, and E) were tested by dropping one or two parameter(s) from the full model. When the submodels and the full model are compared, a significant chi-square difference suggests that the nested model fits significantly worse than the full model and the full model should be chosen; otherwise, the nested model should be considered in terms of parsimony (Bollen, 1989; Kline, 1998). The fit of the nested submodels was also assessed through Akaike's information criterion (Akaike, 1974), and lower AIC values indicate better fit.

We further calculated the proportion of phenotypic correlation (rph) due to correlated genetic effects A (rph-a $= a_1 \times r_g \times a_2$) and correlated non-shared environmental effects E (rph-e $= e_1 \times r_e \times e_2$) expressed as proportions of rph (Fig. 2).

3. Results

3.1. Phenotype correlation between trait impulsivity and rsFC

There was significant correlation between the youth BIS-11 total score and the rsFC between the left full amygdala and right DLPFC, but not the right full amygdala rsFC. The correlation between the youth BIS-11 total score and the rsFC of the amygdala subregions was region-dependent. Specifically, the youth BIS-11 total score was positively correlated with the rsFC of the left BL amygdala in two clusters in the lateral PFC, one in the right middle frontal gyrus or called as DLPFC and the other in the right inferior orbital frontal extending to the orbital frontal gyrus (IFGorb); the youth BIS-11 total score was also positively correlated with the rsFC of the right SF amygdala in the right anterior insula cortex (aINS) and the dorsal anterior cingulate cortex (dACC) (Table 2 and Fig. 3). No other correlations between the youth BIS-11 total score and the rsFC of the amygdala subregions were found (corrected $p < 0.05$).

3.2. Genetic influence on the relationship between trait impulsivity and rsFC

Before investigating the genetic influence on the phenotypic correlation between trait impulsivity and rsFC, we first validated the heritability of trait impulsivity measured using the youth BIS-11 in Chinese twins. The intraclass correlation (ICC) of the youth BIS-11 total score was significantly higher in MZ twins than in DZ twins ($ICC_{MZ} = 0.60$, $ICC_{DZ} = 0.16$, Fisher's z test, one-tailed, $p < 0.001$), suggesting a genetic influence on trait impulsivity. The estimates of univariate genetic modelling are shown in Table 3. The best-fitting model was the AE model, in which 62% of the variation in the youth BIS-11 total score was due to genetic influences and the other 38% was attributed to non-shared environmental influences.

Then, we used the bivariate genetic model to examine the overlapping genetic or environmental influences between trait impulsivity and rsFC. The estimates of cross twin cross trait (ct-ct) correlations for MZ twins' left full amygdala rsFC was relatively higher than that for DZ twins (for MZ: 0.19; for DZ: 0.02), suggesting that the positive correlation between trait impulsivity and left full amygdala rsFC is genetically influenced. For the phenotypic correlation, the bivariate AE model was the best (Table 4), there was large genetic correlations between trait impulsivity and the rsFC of the left full amygdala in the right DLPFC ($r_g = 0.82$ [0.34, 1], Fig. 4A). The proportion of phenotypic association accounted for by overlapping genetic factors (rph-a) was 72% for associations of trait impulsivity with left full amygdala-right DLPFC rsFC (Fig. 4B). We did not find overlap of non-shared environmental influence on the phenotypic association between trait impulsivity and left full amygdala-right DLPFC rsFC, as the confidence interval included zero (Table 5).

The estimates of ct-ct correlations for MZ twins were also relatively higher than those for DZ twins across these rsFCs showing phenotypic correlations with trait impulsivity (for MZ: 0.11–0.17; for DZ: −0.21–0.09), suggesting that the positive correlations between trait impulsivity and the amygdala subregions rsFC are genetically influenced. For all of these phenotypic correlations, the bivariate AE models were the best (Table 4). Specifically, in the bivariate AE model, there were moderate to large genetic correlations between trait impulsivity and the rsFC of the left BL amygdala in the right DLPFC ($r_g = 0.60$ [0.18, 1]) (Fig. 4C). The r_g

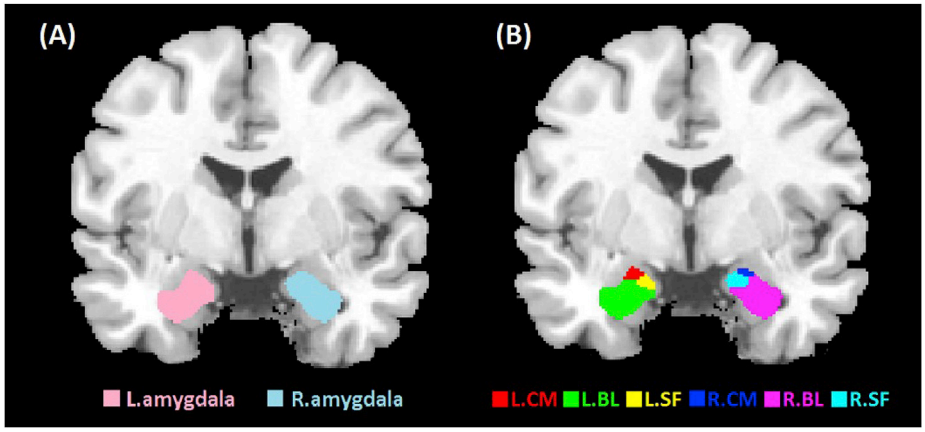

Fig. 1. The amygdala (A) and its subregions (B). These regions were created with the SPM Anatomy Toolbox, registered to MNI space and resampled with a voxel size of $2 \times 2 \times 2\,mm^3$.

confidence interval of the other three rsFCs included zero, which indicated that there is insufficient evidence to support significant genetic correlations between trait impulsivity and the three rsFCs. The rph-a was 64% for associations of trait impulsivity with and the left BL amygdala-right DLPFC rsFC (Fig. 4D). Overlap of non-shared environmental influence was found in the rsFC of the left BL amygdala in the right IFGorb (r_e= 0.31 [0.12,0.48]) and in the rsFC of the right SF amygdala in the right aINS (r_e= 0.21 [0.01,0.4]) and dACC (r_e= 0.28 [0.07,0.46]) (confidence interval did not include zero) (Table 5).

4. Discussion

In a sample of late-adolescent and young adult twins, we found neural correlates of trait impulsivity indicated by its correlation with the rsFC of the amygdala and its subregions, especially in the right DLPFC. We validated that trait impulsivity is under genetic control. More importantly, we found that the phenotypic correlation between trait impulsivity and the rsFCs of both the left amygdala and its left BL subregion with the right DLPFC were partly accounted for by common or overlapping genetic influences.

4.1. The neural correlates of trait impulsivity

Inspired by neuroimaging findings in adults and the theoretical models accounting for impulse control in addiction or risk-taking behavior in adolescence, the current study explored the relationship between the intrinsic functional connectivity of amygdala and its subregions with other brain regions, measured by rsFC, and trait impulsivity in everyday life in late-adolescent and young adult twins. As we hypothesized, the rsFC between the amygdala and the PFC were significantly correlated with trait impulsivity and the correlations were regionally dependent. Specifically, we found that trait impulsivity was positively correlated with the rsFC of the left amygdala with the right DLPFC. While having a closer look on the amygdala subregions, we found the neural correlate of trait impulsivity can be detected in the left BL amygdala. However, trait impulsivity was also positively correlated with the rsFC of the left BL amygdala with the right IFGorb and the rsFC of the right SF amygdala with the dACC. In addition, we found the rsFC between the right SF amygdala and the right aINS correlated with the trait impulsivity. These connections centered at the BL or SF amygdala are consistent with the anatomical projections observed in non-human primate (like rhesus monkeys). For example, there were unidirectional projection from the BL amygdala to the lateral prefrontal cortices (Barbas and De Olmos, 1990; Ghashghaei and Barbas, 2002) and bidirectional connections of the BL amygdala with the orbitofrontal and medial prefrontal cortices (Carmichael and Price, 1995; Ghashghaei et al., 2007; Ghashghaei and Barbas, 2002). In addition, connections from the anterior insula to amygdaloid area including the SF subregion was also observed (Mufson et al., 1981). Work done in animals and humans has furthermore shown that the BL amygdala nuclei might subserve significance detection and associative learning processes through afferent inputs from cortical and subcortical regions, including the thalamus, hippocampus, and prefrontal cortex (Bzdok et al., 2013; Roy et al., 2009). The SF amygdala nuclei are involved in the detection of emotionally salient stimuli and the processing of socially relevant information and social cognition, owing to the extensive bilateral connections with the

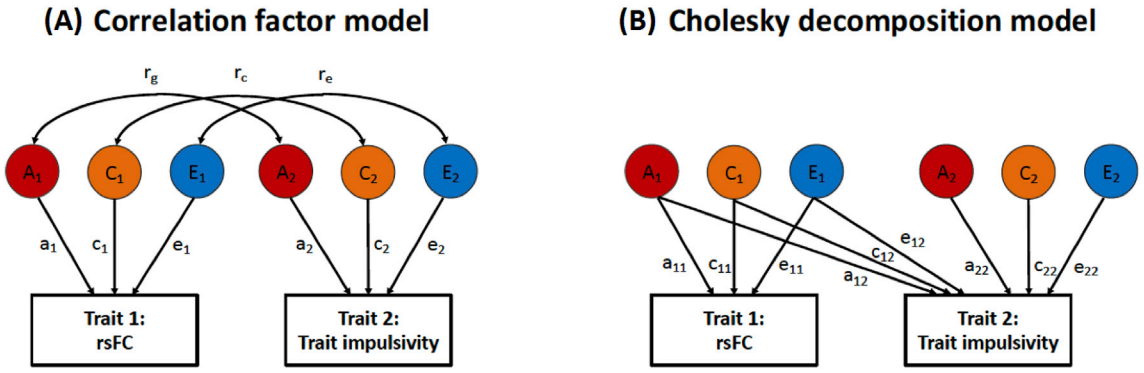

Fig. 2. Bivariate genetic model (A and B) accounting for the correlation between two traits. Two algebraically equivalent representations of the bivariate genetic model are shown: (A) correlated factor solution of genetic correlation (r_g) and non-shared environmental correlation (r_e) and (B) Cholesky decomposition. Latent factors A (genetic factors), C (shared environmental factors) and E (non-shared environmental factors) are in circles.

olfactory cortex, insular cortex, ventral striatum, hippocampus/parahippocampal gyrus and inferior frontal gyrus (Bzdok et al., 2013). The specific localization of the neural correlates of trait impulsivity in the amygdala subregions we found is compatible with the anatomical projections and functional specification of the amygdala subregions.

The total BIS score is a psychometric measure of effortful control that measures two cardinal aspects of impulsivity, i.e., failure to inhibit a prepotent response and short time horizons (Cross et al., 2011). We found positive correlations between the youth BIS-11 total score and the rsFC of the amygdala along with is subregions and the lateral PFC, dACC and aINS, which indicate that the higher the impulsiveness scores, the stronger the intrinsic functional connectivity between the lateral PFC, dACC and aINS regions and the amygdala subregions. In previous studies, negative correlations between trait impulsivity and the rsFCs of the amygdala were reported in adults (Kerr et al., 2015; Ko et al., 2015). However, positive correlations between trait impulsivity and the rsFCs of the amygdala were also suggested. For example, combat veterans who suffer from impulsive aggression were found to have lower negative functional connectivity (i.e., higher functional connectivity) between the BL amygdala and the dorsolateral PFC than veterans without impulsive aggression problems (Varkevisser et al., 2017). A higher rsFC between the amygdala and dACC or insula has also been reported in patients with higher trait impulsivity, such as in drug addiction (Contreras-Rodriguez et al., 2016; Xie et al., 2011), pathological gambling (Contreras-Rodriguez et al., 2016) and borderline personality disorder (Salvador et al., 2016) patients. The neural correlates of trait impulsivity observed in the current study suggest that there is a shifting impulsivity-associated network architecture and neurocircuitry in participants with higher impulsiveness scores. In these nonclinical participants with higher impulsiveness scores, a coordination of affect and cognition may appear more often due to the need for emotion regulation, which is facilitated by the increased connectivity of regions important in the processing of emotional and social information (e.g., the amygdala, aINS) and regions important in cognitive control processes (e.g., the DLPFC, dACC). In a psychophysiological interaction study, the researchers found that amygdala-DLPFC connectivity was positively associated with successful regulation of emotions in healthy controls (Banks et al., 2007). After real-time fMRI neurofeedback training, which could enhance the emotion regulation capability of the subjects, participants' rsFC of the BL and CM amygdala with the prefrontal cortex and rostral anterior cingulate cortex increased significantly (Li et al., 2016). These studies provide support for our view to some extent.

Interestingly, we found that the rsFC of the left amygdala and its BL subregion with the right DLPFC but not in the left one showed significant correlation with trait impulsivity. This contralateral rsFC was not occasionally reported in previous studies (Bzdok et al., 2013; Kerestes et al., 2017; Roy et al., 2009). The recruitment of the right DLPFC in the current study is consistent with previous findings on the right lateralization of the PFC in top-down control over affective impulsive control (Achterberg et al., 2016), response inhibition (Dambacher et al., 2014), and decision making related to impulsivity (Cheng and Lee, 2016; Clark et al., 2003; Knoch et al., 2006). Although it is beyond the scope of this paper to explicitly test it, it is possible that the rsFC between the left amygdala along with its BL subregion and the right DLPFC is an imprint of functional coactivation between these two regions during daily actives to implement impulse control. This possibility needs to be tested in future studies.

Overall, our results support the theoretical models (Bechara, 2005; Ernst, 2014) in which the amygdala-centered circuit is modulated by a cognitive control system centered on the prefrontal cortex to implement impulse control. Furthermore, these findings speak to the importance of examining the amygdala subregions separately rather than treating the amygdala as a unitary structure to better understand the role of amygdala functional specialization in trait impulsivity.

Table 2
Phenotypic correlations between trait impulsivity and resting-state functional connectivity of the amygdala and subregions.

Seed ROI	Target Region	Voxel Size	BA	MNI			Peak T value
				x	y	z	
Full amygdala							
L. amygdala	R. DLPFC[a]	319	9/8/46	54	22	36	4.75
R. amygdala	–						
Amygdala subregions							
L. CM amygdala	–						
R. CM amygdala	–						
L. BL amygdala	R. DLPFC[b]	362	9/46	50	18	30	4.82
	R. IFGorb[c]	192	47/11	36	34	−12	4.51
R. BL amygdala	–						
L. SF amygdala	–						
R. SF amygdala	dACC[c]	287	32/24	−2	16	38	4.30
	R. aINS[c]	250	13/45	30	30	6	4.74

Abbreviations: BA, Brodmann area; MNI, Montreal Neurological Institute; L, left; R, right; rsFC, resting-state functional connectivity; BL, basolateral; SF, superficial; DLPFC, dorsolateral prefrontal cortex; IFGorb, inferior orbital frontal extending to the orbital frontal gyrus; aINS, anterior insula cortex; dACC, dorsal anterior cingulate cortex.

[a] This region survived after a correction for multiple comparisons of the number of seed region (i.e., voxel-level uncorrected $p < 0.001$, Alphasim corrected $p < 0.025 = 0.05/2$ (Bonferroni corrected).

[b] This region survived after a correction for multiple comparisons of the number of seed region (i.e., voxel-level uncorrected $p < 0.001$, Alphasim corrected $p < 0.0083 = 0.05/6$ (Bonferroni corrected).

[c] This region could not survive after a correction for multiple comparisons of the number of seed regions, but passed the threshold of correction for multiple comparisons for voxel-wise HLM analyses (i.e., voxel-level uncorrected $p < 0.001$, Alphasim corrected $p < 0.05$). – None of these regions survived after a correction for multiple comparisons for voxel-wise HLM analyses.

4.2. Genetic overlap between trait impulsivity and amygdala rsFC

Using a twin study design, we further tested the extent to which the associations between trait impulsivity and the rsFC of the amygdala subregions are mediated by shared genetic influences. First, we found that individual differences in trait impulsivity were strongly influenced by genetic factors with minimal shared environmental contributions, which is consistent with previous studies (Bezdjian et al., 2011; Congdon and Canli, 2008; Niv et al., 2012). Then, we found that all of the associations discussed here were due to shared genetic variance between trait impulsivity and rsFC because the AE model was the best model for each association; however, strong support was only found for the associations of trait impulsivity with the rsFC between the left amygdala or its BL subregion and the right DLPFC (confidence intervals did not include zero).

A possible explanation of the genetic correlations is pleiotropy, which means the existence of a common set of genes that influence variance in both trait impulsivity and amygdala rsFC. People with a higher genetic risk for trait impulsivity may also have a genetic propensity for the rsFC of the amygdala outlined here. Genetic association studies have linked several genetic loci with the BIS total score, most notably findings are the genes involved in the dopaminergic and serotonergic pathways (Congdon and Canli, 2008; Dalley and Robbins, 2017; Gray et al., 2018), such as *SLC6A4* (Paaver et al., 2007; Racine et al., 2009; Sakado et al., 2003), *HTR1A* (Benko et al., 2010), *HTR1B* (Varga et al., 2012), *HTR2A* (Preuss et al., 2001; Racine et al., 2009), *DAT1* (Forbes et al., 2009; Paloyelis

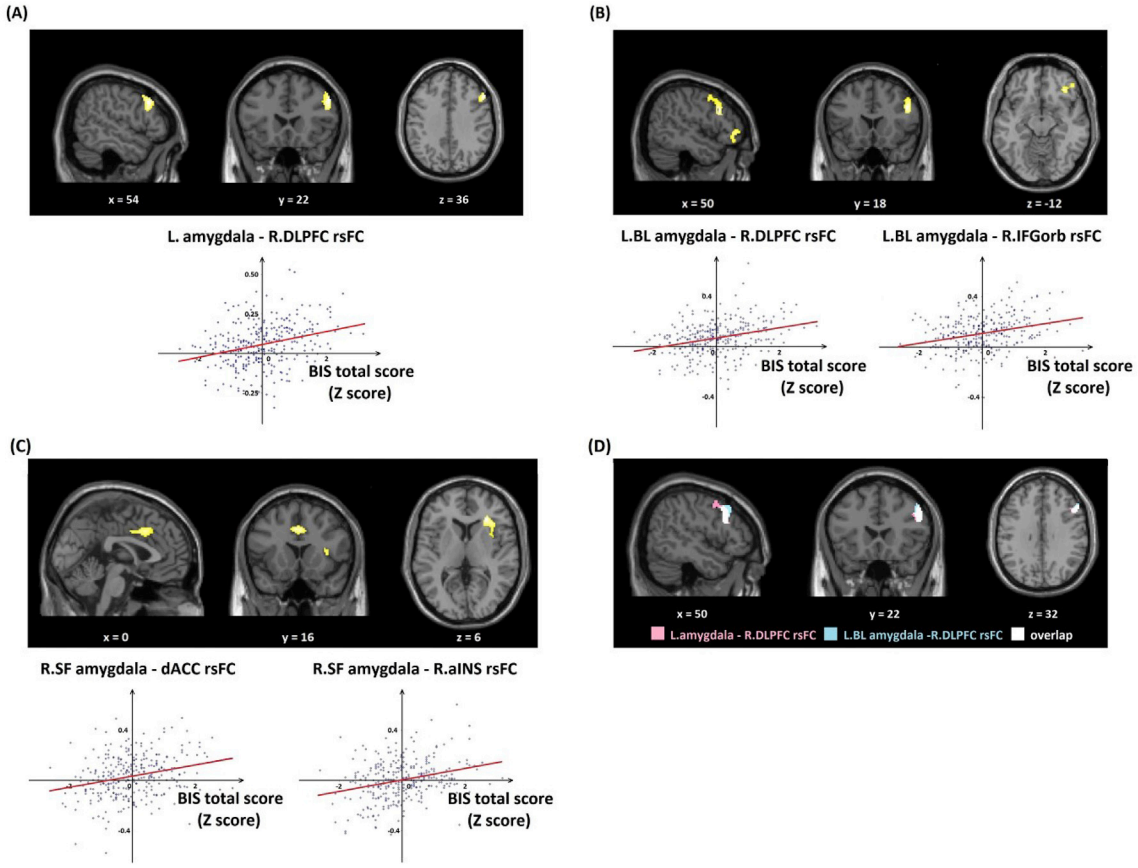

Fig. 3. Phenotypic correlations between trait impulsivity and resting-state functional connectivity of the left full amygdala (A), the left BL amygdala (B) and the right SF amygdala (C), and the overlapped R. DLPFC target region between left full amygdala and left BL amygdala seed ROIs (D).

Table 3
Fit statistics and parameter estimates for the univariate model of trait impulsivity.

Model	-2LL	df	AIC	Change from full model			RMSEA	a2	c2	e2
				Δχ2	Δdf	p				
ACE	833.16	302	229.16				0.078[0.00, 0.16]	0.62[0.40, 0.74]	0.00[0.00, 0.15]	0.38[0.26, 0.55]
AE	833.16	303	227.16	0	1	1	0.066[0.00, 0.14]	0.62[0.45, 0.74]		0.38[0.26, 0.55]
CE	847.54	303	241.54	14.39	1	<0.001	0.133[0.07, 0.20]		0.35[0.20, 0.48]	0.65[0.52, 0.80]
E	867.39	304	259.39	34.23	2	<0.001	0.175[0.12, 0.24]			1.00[1.00, 1.00]

Abbreviations: -2LL, negative 2 log likelihood; df, degrees of freedom; Δdf, difference in degrees of freedom comparing each model to the ACE model; AIC, Akaike information criterion (lower values reflect a better fit); RMSEA, root mean square error of approximation; a^2, proportion of variance due to additive genetic effects (A); c^2, proportion of variance due to shared environmental effects (C); e^2, proportion of variance due to non-shared environmental effects (E). Note: E, CE and AE models are nested within the ACE model. 95% confidence intervals (presented in square brackets) including 0 indicate statistical nonsignificance. The best-fitting model is underlined.

et al., 2010), and *DRD4* (Schilling et al., 2014; Varga et al., 2012). Some of these genes have been linked with the neural networks underlying impulsivity. For example, the 5HTTLPR polymorphism in *SLC6A4* has been associated with altered amygdala responses at rest and in response to aversive stimuli (Hariri et al., 2002, 2005; Long et al., 2013), even though the effect is small (Bastiaansen et al., 2014; Murphy et al., 2013). In terms of impulsivity, a family study of depression found that the 5HTTLPR polymorphism contributed to individual variability in impulse control measured by the Continuous Performance Test through its influence on the connectivity between the default mode network and central executive network (Cha et al., 2018). Although the candidate genes for the neural correlates of trait impulsivity remain unclear, the current evidence suggests that the rsFC of the amygdala may mediate the influences of genes involved in neurotransmitter systems on the inter-individual differences in trait impulsivity. The current evidence further supports the brain-gene association of trait impulsivity and provides a hint for searching for candidate genes for this brain-gene association.

We found that non-shared environmental factors also contribute to the association between trait impulsivity and the rsFC of the amygdala, with strong evidence for the rsFC of the left BL amygdala in the right IFGorb and in the rsFC of the right SF amygdala in the right aINS and dACC. Evidence from studies on the neurodevelopment of the adolescent brain has shown that the myelination and pruning of the PFC continues into adulthood (Casey et al., 2008; Romer et al., 2017; Steinberg, 2008). The circuits of the developing PFC are sculpted on the basis of its exposure to a wide range of environmental events, including parental-child relationships, peer relationships, early stress, hormones, and sensory stimuli (Kolb et al., 2012). And the influence of negative environmental factors in fetal period and youths (such as prenatal maternal depression and traumatic exposure) may influence the normal development of amygdala functional connectivity which is critical for the emotional

Table 4
Fittting statistics and parameter estimates for the bivariate model of trait impulsivity and resting-state functional connectivity (rsFC).

rsFC	Model	-2LL	df	AIC	Change from full model			RMSEA
					$\Delta\chi^2$	Δdf	p	
Full amygdala								
L. amygdala - R. DLPFC	ACE	1596.12	573	450.12				0.054[0.00, 0.11]
	AE	1596.12	576	444.12	0	3	1	0.038[0.00, 0.09]
	CE	1610.10	576	458.10	13.98	3	0.003	0.079[0.03, 0.12]
	E	1628.24	579	470.24	32.12	6	<0.001	0.100[0.06, 0.14]
Amygdala subregions								
L. BL amygdala - R. DLPFC	ACE	1574.79	572*	430.79				0.053[0.00, 0.11]
	AE	1575.10	575*	425.10	0.31	3	0.96	0.038[0.00, 0.09]
	CE	1588.45	575*	438.45	13.65	3	0.003	0.077[0.03, 0.12]
	E	1608.35	578*	452.35	33.56	6	<0.001	0.101[0.06, 0.14]
L. BL amygdala - R. IFGorb	ACE	1593.70	573	447.70				0.042[0.00, 0.10]
	AE	1594.07	576	442.07	0.37	3	0.95	0.024[0.00, 0.08]
	CE	1607.06	576	455.06	13.36	3	0.004	0.071[0.01, 0.12]
	E	1628.74	579	470.74	35.04	6	<0.001	0.100[0.06, 0.14]
R. SF amygdala - R. dACC	ACE	1604.05	573	458.05				0.073[0.00, 0.12]
	AE	1604.05	576	452.05	0	3	1	0.062[0.00, 0.11]
	CE	1617.73	576	465.73	13.69	3	0.003	0.092[0.05, 0.13]
	E	1636.03	579	478.03	31.98	6	<0.001	0.116[0.08, 0.15]
R. SF amygdala - R. aINS	ACE	1595.69	573	449.69				0.043[0.00, 0.10]
	AE	1595.69	576	443.69	0	3	1	0.023[0.00, 0.08]
	CE	1609.75	576	457.75	14.05	3	0.003	0.073[0.02, 0.12]
	E	1629.26	579	471.26	33.57	6	<0.001	0.098[0.06, 0.14]

Note: * one participant's rsFC value exceeded three standard deviations and thus was excluded. For abbreviations: please see also Tables 2 and 3.

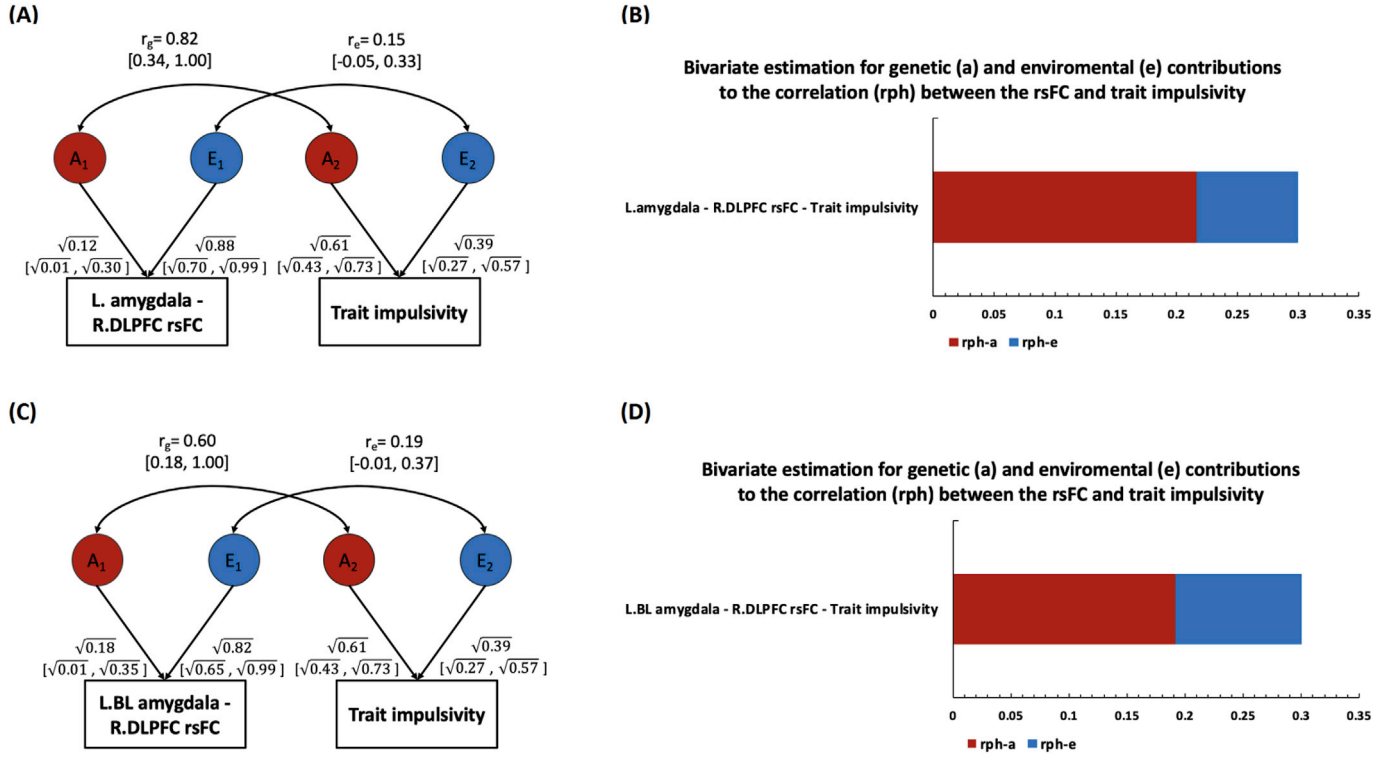

Fig. 4. Bivariate genetic/environmental correlation modelling of trait impulsivity and resting-state functional connectivity (rsFC) of the left full amygdala and the left BL amygdala. The genetic (r_g) and environmental (r_e) correlations between trait impulsivity and rsFC are shown in (A) for the left full amygdala and in (C) for the left BL amygdala. The bivariate estimation for genetic (rph-a) and non-shared environmental (rph-e) contributions to the correlation between trait impulsivity and the rsFC (the length of the bar) are shown in (B) for the left full amygdala and in (D) for the left BL amygdala. Here, rph-a = $a_1 \times r_g \times a_2$, and rph-e = $e_1 \times r_e \times e_2$.

regulation process (Richmond et al., 2016). Interventions on non-shared environmental factors could likely influence both trait impulsivity and brain function. An example of these factors is peer relationships. As individuals enter adolescence and early adulthood, peers can exert great influence on individuals' opinions and behaviors. Peer relationships have been found to moderate cognitive impulsivity (Menting et al., 2016) and influence PFC plasticity (Kolb et al., 2012).

Several limitations should be mentioned. First, the measurement of trait impulsivity used in this study is a version adapted specifically for adolescents. Although the reliability of this score is acceptable based on the estimation, the validity has not been proven before. Thus, the results must be cautiously interpreted due to the measuring instruments used.

Table 5
Parameter estimates for the bivariate AE model for trait impulsivity and resting-state functional connectivity.

Variables	Parameter estimates for rsFC		Parameter estimates for the correlations between trait impulsivity and rsFC				
	a^2[CI]	e^2[CI]	r_g[CI]	r_e[CI]	rph [CI]	rph-a [CI]	rph-e [CI]
Full amygdala							
L. amygdala –R. DLPFC	0.12[0.01, 0.30]	0.88[0.70,0.99]	**0.82 [0.34, 1.00]**	0.15[-0.05, 0.33]	0.30[0.19, 0.41]	0.72[0.28 1.00]	0.28[-0.11, 0.72]
Amygdala subregions							
L. BL amygdala –R. DLPFC	0.18[0.01,0.35]	0.82[0.65,0.99]	**0.60 [0.18, 1.00]**	0.19[-0.01, 0.37]	0.30[0.19, 0.41]	0.64[0.17, 1.00]	0.36[-0.02, 0.83]
L. BL amygdala –R. IFGorb	0.13[0.00,0.31]	0.87[0.69,1.00]	0.41[-1.00, 1.00]	**0.31 [0.12, 0.48]**	0.30[0.18, 0.40]	0.38[-0.16, 0.77]	0.62[0.23, 1.00]
R. SF amygdala –R. dACC	0.24[0.04,0.42]	0.76[0.58,0.96]	0.31[-0.11, 0.75]	**0.28 [0.07, 0.46]**	0.27[0.15, 0.38]	0.44[-0.18, 0.86]	0.56[0.14, 1.00]
R. SF amygdala –R. aINS	0.18[0.01, 0.36]	0.82[0.64,0.99]	0.53[-0.10, 1.00]	**0.21 [0.01, 0.40]**	0.30[0.18, 0.40]	0.59[0.11 0.98]	0.41[0.18, 0.89]

Abbreviations: CI, 95% confidence intervals; r_g, genetic correlation; r_e, non-shared environmental correlation; rph, phenotypic correlation; rph-a, the proportion of phenotypic correlations explained by overlapping genetic factors; rph-e, the proportion of phenotypic correlations explained by overlapping non-shared environmental factors. For other abbreviations, please see also Tables 2 and 3.

Second, the cross-sectional nature of the dataset indicates that the causality between trait impulsivity and resting-state functional connectivity is suggestive. A longitudinal design would provide better insight into the causal associations between brain function and trait impulsivity. Moreover, resting-state functional connectivity changes across the lifespan (Zuo et al., 2017), but impulsivity decreases with age during the second decade of life and may remain stable in adulthood (Shulman et al., 2016). Thus, to establish a full picture of how genetic and environmental factors affect the association between trait impulsivity and brain function, both cross-sectional and longitudinal data across the lifespan are needed.

In summary, the present study provides important evidence that inter-individual differences in trait impulsivity are correlated with the resting-state functional connectivity between the left amygdala as well as its BL subregion and the right DLPFC. More importantly, the phenotypic correlations are partly due to shared genetic factors. This finding will facilitate the discovery of gene variants that influence trait impulsivity and advance our understanding of the biological basis of impulsive behavior with potential adverse consequences in adolescence and young adults, in whom trait impulsivity plays an important role.

Declarations of interest

The authors declare no conflict of interest of any kind.

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