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Parental Warmth, Stressful Life Events, and Impulsivity: A Gene–Environment-Wide Interaction Study

Xinrui Wang[1], Hejun Liu[1], Qinghua He[2], Chuansheng Chen[3], Gui Xue[1], Qi Dong[1], and Chunhui Chen[1]

[1] State Key Laboratory of Cognitive Neuroscience and Learning, IDG/McGovern Institute for Brain Research, Beijing Normal University

[2] Faculty of Psychology, Southwest University

[3] Department of Psychological Science, University of California, Irvine

Objective: Impulsivity is influenced by genetic, neural, and environmental factors, but no study has examined how these factors work together to generate individual differences in impulsivity. The present study aimed to define the functional network that subserves impulsivity and test its relations with the gene–environment interactions found in the gene–environment-wide interaction study. ***Method:*** This study used a sample of healthy Chinese college students ($N = 1,145$) to identify gene–environment interactive effects on impulsivity, then defined the functional brain network related to impulsivity in an independent sample ($N = 483$), and explored the gene–brain associations using polygenic risk score. ***Results:*** The present study found that 14 genes showed significant interactive effects with parental warmth (a protective environmental factor) and that six genes showed significant interactive effects with stressful life events (a risk environmental factor). The polygenic risk score for parental warmth was significantly correlated with functional connectivity especially the left middle frontal gyrus (MFG)-left inferior occipital and left MFG-left superior frontal gyrus functional connectivity, while the polygenic risk score for more stressful life events was significantly correlated with functional connectivity of left dorsal medial prefrontal cortex (DMPFC) to other regions. These associations were stronger in more adverse environments (i.e., low parental warmth or high stressful life events). ***Conclusions:*** This was the first gene–environment-wide interaction study of impulsivity. Future studies should replicate our results and explore the underlying mechanisms of these interactions.

Key Points

Question: How do genetic, neural, and environmental factors work together to generate individual differences in impulsivity? ***Findings:*** Protective (parental warmth) and risk (stressful life events) environmental factors can modulate distinct genetic effects on impulsivity through different neural mechanisms. ***Importance:*** Life adversity (like stress) needs to be taken into consideration to reduce impulsivity. ***Next Steps:*** Future studies should replicate our results and explore the underlying mechanisms of these interactions.

Keywords: impulsive, gene–environment-wide interaction study, parental warmth, stressful life event

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Impulsivity refers to a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions (McHugh et al., 2019; Moeller et al., 2001). It is usually measured with the delay discounting (DD) task that assesses a person's relative preference for small immediate rewards versus larger delayed rewards (MacKillop et al., 2015). Individual differences in DD have been found to show significant heritability, but genetic studies have not consistently identified relevant genes (Anokhin et al., 2011; Isen et al., 2014; Sparks et al., 2014). Earlier candidate gene studies focused on neurotransmitter-related genes such as catechol-O-methyltransferase, ankyrin repeat and kinase domain containing 1, dopamine receptor D4,

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Xinrui Wang and Hejun Liu contributed equally to this work.

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Correspondence concerning this article should be addressed to Chunhui Chen, State Key Laboratory of Cognitive Neuroscience and Learning, IDG/McGovern Institute for Brain Research, Beijing Normal University, 19# Xinjiekouwai Street, Beijing 100875, China. Email: chenchunhuichina@bnu.edu.cn

and adrenoceptor alpha 2A (Boettiger et al., 2007; Eisenberg et al., 2007; Havranek et al., 2017; MacKillop et al., 2015; C. T. Smith & Boettiger, 2012; Sweitzer et al., 2013). Recent genome-wide association studies identified genes such as glycoprotein M6B, which is involved in the internalization of the serotonin transporter (Sanchez-Roige, Fontanillas, et al., 2018), and rs13395777, which is located on an intergenic region of chromosome 2 with unknown function (MacKillop et al., 2019).

Impulsivity is also influenced by many environmental factors, as well as their interactions with genes. Stressful life events are risk factors (DeAngelis et al., 2022; Fields et al., 2014; Lempert et al., 2012), whereas parental warmth is a protective factor (He et al., 2012; Kahn et al., 2015). Gene–environmental interaction on DD has also been reported. Individuals with low socioeconomic status who carried the dopamine receptor D4 7-repeat allele discounted future rewards more steeply than the counterparts who had no copies of the 7-repeat allele (Sweitzer et al., 2013). We further found that parental warmth and stressful life events showed different interaction patterns with catechol-O-methyltransferase on decision making: Catechol-O-methyltransferase Met carriers displayed more reward sensitivity (i.e., more sensitive to gains) if they experienced higher stress, while Val/Val homozygotes are less reward sensitive if they experienced higher parental warmth (He et al., 2012). Instead of using candidate genes, recent researches relied on the gene–environment-wide interaction study (GEWIS). We have used that approach successfully to identify gene–environment interactions on cognition such as executive functions and working memory (C. Chen et al., 2020, 2021). The present study used the same GEWIS approach to study impulsivity.

In addition to GEWIS, this study also included imaging genetics using an independent sample to explore relevant neural mechanisms. Many brain regions, including sensory, memory, motivation/emotion, and reward networks, have been reported to be associated with DD (Frost & McNaughton, 2017). According to the β–δ model, the β system is responsible for the evaluation of the immediate rewards and its neural network consists of the nucleus accumbens, subgenual cingulate cortex, medial orbitofrontal cortex, posterior cingulate cortex, dorsal anterior cingulate cortex, and precuneus, whereas the δ system is responsible for the value of more delayed rewards and its neural network consists of the lateral control regions such as the bilateral areas in the posterior parietal cortex, bilateral areas in the anterior insula, and several regions in the dorsolateral prefrontal cortex (McClure et al., 2007). A previous study using our cohort found that gray matter volume in the frontal pole (FP) and middle frontal gyrus (MFG; Q. Wang et al., 2016), as well as resting state brain activity in the dorsal medial prefrontal cortex (DMPFC; Lv et al., 2019), was associated with DD performance. All of the above regions belong to the δ system. Since brain functional connectivity was found to be highly heritable (Adhikari et al., 2018; Ge et al., 2017), and in order to capture the brain networks of impulsivity modulated by gene and environment interaction, the present study used these regions as seeds to define the functional network that subserves impulsivity and test its relations with the gene–environment interactions found in the GEWIS.

Method

Participants

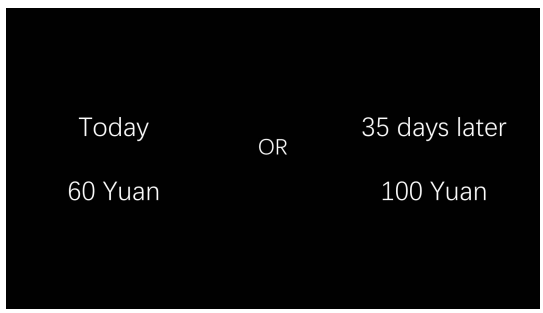
This study included two independent samples of data. The first sample was used to test the gene–environment–behavior associations, and the second sample was used to test the underlying brain mechanisms. The first sample included 1,145 healthy Chinese college students (711 females, M_{age} = 20.21 years and SD = 1.94, ranging from 16 to 30) from Beijing Normal University and Southwest University. They completed both genotyping and behavioral tests, but no brain imaging data were collected. Because some subjects had not finished the environmental scales, 1,047 subjects (633 females, M_{age} = 20.39 years and SD = 1.97, ranging from 17 to 30) were included in the parental warmth by gene interaction analysis, and 1,045 (632 females, M_{age} = 20.39 years and SD = 1.97, ranging from 17 to 30) included in stress by gene interaction analysis. The second sample included 483 college students from Beijing Normal University (246 females, M_{age} = 21.41 years and SD = 2.25, ranging from 17 to 29) who had valid behavioral, genetic, and brain imaging data. Participants in both samples were provided information on campus by flyer and were subsequently enrolled. Only Han Chinese that self-reported no history of psychiatric disease, head injury, or stroke/seizure were included. This study was approved by the institutional review board (IRB) of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University, China. After a full explanation of the study procedure, written consent was obtained from each participant.

Behavioral Measures

Decision Impulsivity Task

This task has been described in previous publications (Lv et al., 2019; Q. Wang et al., 2016). Briefly, subjects were presented with a choice between a fixed immediate reward (Chinese Yuan (CNY ¥) 60, approximately United States dollar 10, paid today) and a varied delayed reward (CNY 78–108, approximately United States dollar 13–18, to be paid in 15–45 days) and had to choose a preferred one (Figure 1). There are 60 trials in total, with the amount and time of the delayed reward adaptively changing according to their choice. We assumed a hyperbolic function $SV = \frac{A}{(1+k*D)}$ for temporal discounting, where SV is the subjective value, A is the reward magnitude, D is the delay time, and k is the delay discounting rate. The initial discounting rate was set to 0.02 and was increased when the participants chose the immediate reward, but decreased when they chose the delayed reward. For the first 20 trials, the step size for

Figure 1
Adaptive Delay Discounting Task



Note. For each trial, subjects had to choose between a fixed reward (¥60) and a larger later reward. The delay period for the larger later reward was randomly chosen from ¥78 to ¥108 between 15 and 45 days in the future.

the change of k was set to 0.01 and after that, the step size decreased by 5% of the previous k value for each following step. Following previous studies (Johnson & Bickel, 2002; Lagorio & Madden, 2005), hypothetical money was used to serve as a valid proxy for real money. Because of the skewed distribution of the delay discounting rates, a log-transformed k (log k) was used to represent impulsive choice, with a larger value indicating higher impulsivity (Lv et al., 2019; Q. Wang et al., 2016).

Environmental Measures

There were two environmental measures, one risk factor and one protective factor. The Stressful Life Events Scale (SLES) was used to measure chronic stress (Beam et al., 2002). Chronic stress was chosen because previous studies have shown that naturally occurring stressors have severe impacts on impulsivity (Brooks et al., 2017; Fields et al., 2014; Watt et al., 2017). The SLES is a 24-item questionnaire about stressful family and peer events. Examples are "the death of a close friend" and "a parent became seriously ill." Subjects were asked to indicate if that problem happened to him/her one or more times during college life. The total score for this scale was the number of stressful events experienced. Thus, a higher score represents more stressful event exposure. To assess the protective factor, the Parental Warmth Scale (PWS), modified from Greenberger and Chen et al., was used (Greenberger & Chen, 1996; Greenberger et al., 1998). The PWS is an 11-item questionnaire regarding subjects' parents, including questions such as "my parents really enjoy spending time with me." Subjects were asked to rate their agreement with those statements from 1 (*strongly disagree*) to 6 (*strongly agree*). The total ratings of all 11 items were summed.

Genotyping

Detailed procedures of genotyping for this data set were reported in previous publications (C. Chen et al., 2020, 2021). Briefly, DNA was extracted from blood samples and genotyped using Infinium chips (Illumina, San Diego, CA, USA) according to the manufacturer's specifications. Autosome genotype data were cleaned with PLINK 1.9 (https://www.cog-genomics.org/plink/1.9/; Chang et al., 2015) and then imputed using Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html#!) following their protocol using 1,000 G Phase 3 East Asian population as reference. Imputed data were cleaned again, retaining 4,856,474 Single Nucleotide Polymorphisms (SNPs). No duplicated or related subjects were identified (maximum relatedness PI_HAT = 0.0537, calculated with PLINK). No clear population stratification problem or outlier subjects were found by principal component analysis, most likely because this study only enrolled Han Chinese subjects (C. Chen et al., 2020).

Brain Imaging Acquisition and Preprocessing

Brain images were acquired using a Siemens Trio 3T scanner in the Brain Imaging Center of Beijing Normal University. Foam pads were used to minimize head motion. Resting state functional images were acquired with single-shot T2*-weighted gradient-echo Echo planar imaging sequence, with the following parameters: repetition time/echo time/flip angle = 2,000 ms/30 ms/90°, field of view = 200 × 200 mm, matrix = 64 × 64, and slice thickness = 3.5 mm. Forty-one interleaved axial slices parallel to the anterior commissure–posterior commissure line (AC–PC line) were obtained to cover the whole brain. A series of 200 images were acquired. Structural MRI images were acquired for registration purpose using a T1-weighted, three-dimensional, gradient-echo pulse sequence. Parameters for this sequence were as follows: repetition time/echo time/flip angle = 2,530 ms/3.39 ms/7°, field of view = 256 × 256 mm, matrix = 256 × 256, and slice thickness = 1.33 mm. One hundred forty-four sagittal slices were acquired to provide a high-resolution structural image of the whole brain.

Resting state functional images were preprocessed using the GRaph thEoreTical Network Analysis (GRETNA) toolbox (J. Wang et al., 2015) and the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996) as described before (Feng et al., 2020). Steps included removing the first 10 volumes, slice timing correcting, realignment, coregistering and normalizing to the standardized MNI space, linear detrending, nuisance regression (head motion, white matter signal, Cerebro-Spinal Fluid signal, and global signal), and temporal band-pass filtering (0.01–0.08 Hz). Visual inspection was taken after each step and all had good quality. Right FP (MNI [16 40 38]), left MFG (MNI [−50 34 34]), and left DMPFC (MNI [−4 42 14]) reported in previous studies (Lv et al., 2019; Q. Wang et al., 2016) were used to define regions of interest (ROI) of DD as 5-mm radius spheres. Functional connectivity (FC) between these ROIs and the whole brain was calculated as Pearson correlations between the time course of each voxel and the mean time course of each ROI, then transformed into z scores by Fisher's formula. These FC maps were used for further analysis.

Statistical Analyses

GEWIS analysis was run using PLINK linear regression, using log k as the dependent variable; one of the two environment variables, genotype, and their interaction as independent variables; and age, sex, and first 10 principal components of the genome as covariates. The conventional GWAS threshold of 5 E-8 was applied.

GEWIS results were inputted into Multi-marker Analysis of GenoMic Annotation (de Leeuw et al., 2015) for gene set enrichment analysis. Gene definition was downloaded from the MAGMA website (https://ctg.cncr.nl/software/magma), using the NCBI 37.3 Version, resulting in 17,287 genes. The sum of –log(p) within a gene was calculated as the gene-level statistics (MAGMA default model). Bonferroni correction was applied, with the threshold of p = .05/17,287 = 2.89 E-6.

To explore gene–brain associations, polygenic risk scores (PRSs) were calculated on the imaging genetics sample using PRSice (https://choishingwan.github.io/PRSice/; Choi & O'Reilly, 2019). The GEWIS summary statistics, as well as the genotype and DD performance of the imaging genetics sample, was inputted into PRSice to calculate gene scores at p < 5e-2, 5e-3, 5e-4, 5e-5, 5e-6, 5e-7, 5e-8, respectively. Gene scores of significant genes identified by MAGMA were also calculated using PLINK. Variants within the gene regions were first clumped with PLINK (–clump-p1 0.01 –clump-p2 0.05 –clump-r2 0.50 –clump-kb 250) to select the most significant independent variant iteratively. The resulting independent SNPs were used to calculate gene score defined as the sum of allele counts (coded as 0/1/2), weighted by estimated effect sizes obtained from GEWIS (β in PLINK results; Wray et al., 2014). These PRSs were regressed on the FC maps of the right FP, left MFG, and left DMPFC separately using FMRIB's Software Library (FSL) for Linux (https://fsl.fmrib.ox.ac.uk/fsl). The resulting maps were corrected with

Gaussian random field (GRF) correction, with the voxel-level threshold of $p < .001$ and the cluster-level threshold of $p < .05$.

Transparency and Openness

We report how we determined participants, exclusions, and measures, and we follow American psychological association Journal Article Reporting Standards (JARS). This study's design and analysis were not preregistered. All data are available on request.

Results

Behavioral Performance

Means and standard deviations of DD performance, parental warmth, and stressful life events are shown in Table 1. Parental warmth and stressful life events were negatively correlated ($r = -0.192$, $p < .01$). The two environmental factors were not significantly associated with DD performance.

Gene–Environment-Wide Interaction on DD

GEWIS analysis identified many loci with main and/or interaction effects with parental warmth on DD performance (Figure 2, left). For stressful life events, no SNP showed significant main effect, but some showed significant interactions on DD performance (Figure 2, right). MAGMA analysis showed that 14 genes (*PNPT1*, *COBLL1*, *SLC7A14*, *TMEM144*, *CTNND2*, *SUSD1*, *CTNNA3*, *SNX29*, *RFWD3*, *MLKL*, *CCL14*, *CACNG5*, *SDCBP2*, *C2CD2*) significantly interacted with parental warmth and six genes (*HSPB11*, *LRRC42*, *RHOV*, *VPS18*, *CACNG5*, *SDCBP2*) significantly interacted with stressful life events on DD (Table 2). In addition, some genes showed only significant main effects but no interactions with parental warmth on DD (Table 2).

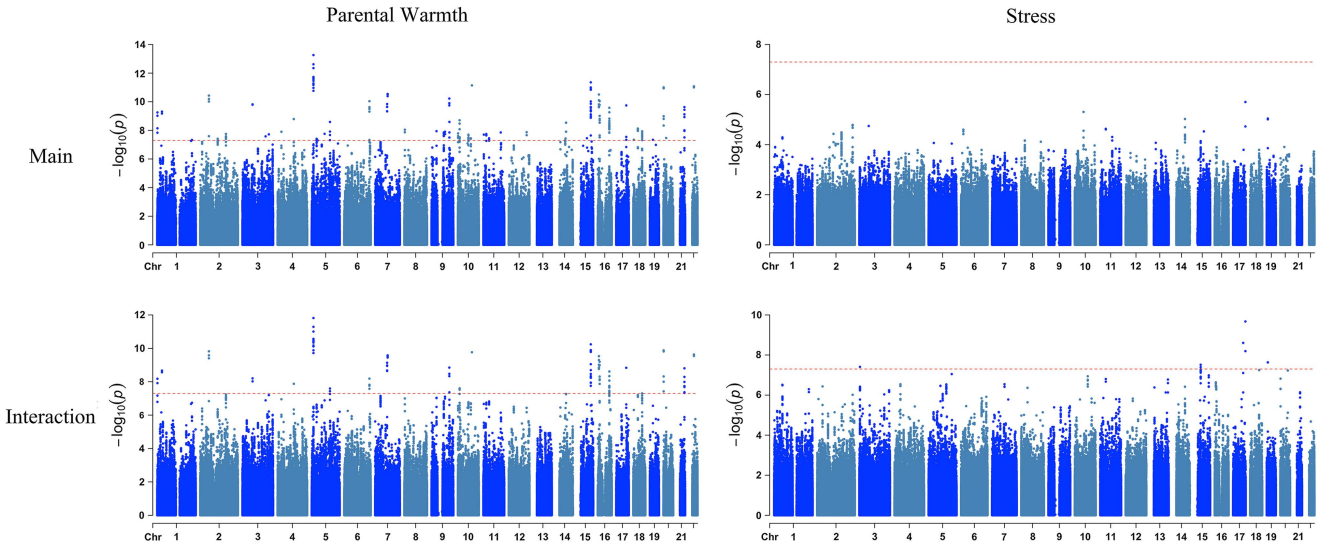
Table 1
Means and Standard Deviations of Behavioral Measurements

Behavioral measurements	*M*	*SD*
Delay discounting	−2.197	1.079
Parental warmth	51.3	8.744
Stressful life events	2.63	2.362

Gene–FC Association

To examine how these genes interacted with environmental factors on impulsivity-related brain regions, we calculated PRS based on genes that significantly interacted with parental warmth or stressful life events at different thresholds and then associated these PRSs to resting state FC maps generated using the right FP, left MFG, and left DMPFC as seeds. As shown in Table 3, PRSs for genes interacting with parental warmth were associated with a lot of brain functional connectivity, including right FP to bilateral fusiform gyrus and bilateral middle occipital, left MFG to bilateral inferior occipital and left superior frontal gyrus, and left DMPFC to right inferior and middle frontal gyrus. PRSs calculated at different thresholds captured distinct genetic effects, with looser thresholds capturing more genetic effects but also more noise, which may contribute to different brain regions. Still, the left MFG-left inferior occipital and

Figure 2
Manhattan Plot of Main and Interaction Effects of Genes and Environmental Factors on Delay Discounting



Note. Each dot represents the effect of a SNP, with the *y*-axis the -log10 transformed *p* value of the effect. SNPs are aligned on the *x*-axis based on their position on each chromosome. The red dotted line represents $p = 5E\text{-}8$. The dots above the red lines are the significant effects. SNP = Single Nucleotide Polymorphism. See the online article for the color version of this figure.

Table 2
Genes That Showed Significant Main and/or Interaction Effects With Environmental Factors on Delay Discounting Identified by MAGMA

Environment	Gene	CHROMOSOME	START	STOP	Z	*P*-inter	*P*-main
Parental warmth	*PNPT1*	2	55861198	55921045	5.6072	4.97 E-08	1.03 E-08
Parental warmth	*COBLL1*	2	165536695	165698678	5.2751	7.19 E-08	6.63 E-08
Parental warmth	*SLC7A14*	3	170177342	170303863	4.7654	1.55 E-06	9.42 E-07
Parental warmth	*TMEM144*	4	159122749	159176439	5.1559	8.83 E-07	1.26 E-07
Parental warmth	*CTNND2*	5	10971952	11904155	7.4254	7.51 E-13	5.62 E-14
Parental warmth	*SUSD1*	9	114803061	114937577	5.3132	1.81 E-07	5.39 E-08
Parental warmth	*CTNNA3*	10	67672276	69455949	5.3456	2.30 E-07	4.51 E-08
Parental warmth	*SNX29*	16	12070602	12668146	5.4228	2.77 E-06	2.93 E-08
Parental warmth	*RFWD3*	16	74655297	74700779	5.4927	1.66 E-07	1.98 E-08
Parental warmth	*MLKL*	16	74705753	74734789	4.9737	1.13 E-06	3.28 E-07
Parental warmth	*CCL14*	17	34310692	34313764	4.8538	1.40 E-06	6.06 E-07
Parental warmth	*CACNG5*	17	64831235	64881941	5.6037	4.25 E-07	1.05 E-08
Parental warmth	*SDCBP2*	20	1290553	1309879	6.3461	2.94 E-10	1.10 E-10
Parental warmth	*C2CD2*	21	43305219	43374066	4.8621	2.89 E-06	5.81 E-07
Parental warmth	*FYB*	5	39105354	39270759	4.6867	—	1.39 E-06
Parental warmth	*CD36*	7	80231504	80308593	4.5568	—	2.60 E-06
Parental warmth	*PRUNE2*	9	79226292	79521136	5.013	—	2.68 E-07
Parental warmth	*SET*	9	131445934	131458675	4.7681	—	9.30 E-07
Parental warmth	*ZER1*	9	131492065	131534220	4.6809	—	1.43 E-06
Parental warmth	*CELF2*	10	10838851	11378674	4.598	—	2.13 E-06
Parental warmth	*STAMBPL1*	10	90639597	90735343	4.74	—	1.07 E-06
Parental warmth	*ACTA2*	10	90694831	90751147	5.1095	—	1.62 E-07
Parental warmth	*AKAP13*	15	85923818	86292589	5.2631	—	7.08 E-08
Parental warmth	*RBFOX1*	16	5289469	7763342	5.4649	—	2.32 E-08
Parental warmth	*GLG1*	16	74481325	74641042	4.6053	—	2.06 E-06
Parental warmth	*DLGAP1*	18	3496030	4455310	4.7943	—	8.16 E-07
Parental warmth	*CCBE1*	18	57098171	57364860	4.5353	—	2.88 E-06
Stressful life events	*HSPB11*	1	54387234	54411975	4.7827	8.65 E-07	—
Stressful life events	*LRRC42*	1	54411999	54433841	4.7301	1.12 E-06	—
Stressful life events	*RHOV*	15	41164412	41166487	4.9606	3.51 E-07	—
Stressful life events	*VPS18*	15	41186628	41196173	4.8133	7.42 E-07	—
Stressful life events	*CACNG5*	17	64831235	64881941	4.6449	1.70 E-06	—
Stressful life events	*SDCBP2*	20	1290553	1309879	4.6906	1.36 E-06	—

Note. MAGMA = Multi-marker Analysis of GenoMic Annotation.

left MFG-left superior frontal gyrus were consistently identified by PRSs calculated at different thresholds (Figure 3). Similarly, PRSs for genes interacting with stressful life events were also associated with a lot of brain functional connectivity, including left DMPFC to left inferior temporal gyrus, right middle temporal gyrus, left caudate, and right frontal orbital cortex; right FP to left frontal pole (Table 3), indicating that functional connectivity of DMPFC might tend to be modulated by stress (Figure 3).

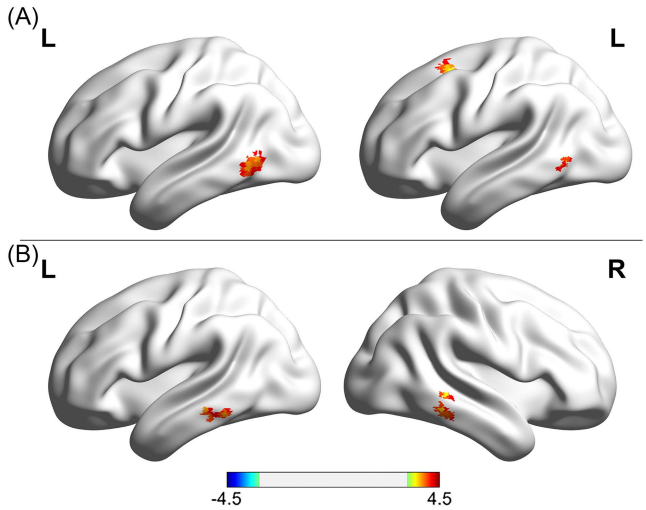
Table 3
Resting State Functional Connectivity Significantly Correlated With PRS

Environmental factor	Threshold	Seed	Connected areas	Cluster size	*T* value	MNI coordinates
Parental warmth	5.00 E-02	Right FP	Right fusiform gyrus	68	−4.47	21 −84 −6
			Left fusiform gyrus	49	−4.24	−21 −75 −6
			Right middle occipital	42	−4.02	30 −78 3
			Left middle occipital	32	−3.96	−27 −87 9
	5.00 E-03	*Left MFG*	*Left inferior occipital*	34	3.66	−60 −66 −6
	5.00 E-04	*Left MFG*	*Left inferior occipital*	127	6.53	−57 −69 −6
			Right inferior occipital	50	4.4	54 −66 −6
	5.00 E-05	*Left MFG*	*Left inferior occipital*	41	4.28	−48 −57 −3
			Left superior frontal gyrus	34	4.44	−24 9 54
	5.00 E-06	*Left MFG*	*Left superior frontal gyrus*	40	4.19	−21 0 51
	5.00 E-08	*Left MFG*	*Left superior frontal gyrus*	28	3.94	−24 3 51
		Left DMPFC	Right inferior frontal gyrus	29	−4.97	30 24 24
	14 significant genes	Left DMPFC	Right middle frontal gyrus	64	−4.37	39 0 60
Stressful life events	5.00 E-04	Left DMPFC	Left inferior temporal gyrus	35	3.92	−66 −42 −18
	5.00 E-04	Left DMPFC	Right middle temporal gyrus	34	4.49	63 −39 −15
	5.00 E-07	Right FP	Left frontal pole	80	4.87	−42 36 15
	Six significant genes	Left DMPFC	Left caudate	32	4.19	−3 15 3
			Right frontal orbital cortex	35	−3.88	36 30 −3

Note. Brain regions in italic are those consistent across PRS calcualted at mutiple thresholds. FP = frontal pole; PRS = polygenic risk score; MFG = middle frontal gyrus; DMPFC = dorsal medial prefrontal cortex.

Figure 3

Resting State Functional Connectivity Significantly Correlated With PRS



Note. Resting state FC of left MFG to left inferior occipital and left superior frontal gyrus significantly correlated with PRS for genes interacting with parental warmth (A), and FC of left DMPFC to left inferior temporal gyrus and right middle temporal gyrus significantly correlated with PRS for genes interacting with stressful life events (B). The colorful clusters showed the brain regions with significant association with PRSs, with red representing positive correlation and blue representing negative correlation. FC = functional connectivity; PRS = polygenic risk score; MFG = middle frontal gyrus; DMPFC = dorsal medial prefrontal cortex. See the online article for the color version of this figure.

To further explore the interactions, we divided subjects into low, medium, and high stressful life events/parental warmth groups with approximately the same group size (for parental warmth, n = 168/169/146, respectively; for stressful life events, n = 166/181/136, not exactly the same size because some individuals had the same score), and explored the PRS-FC associations for each group. All PRS-FC associations listed in Table 3 showed a similar pattern, as illustrated in Figure 4 for the left MFG-left inferior occipital FC and the left MFG-left superior frontal gyrus FC for PRS of parental warmth, and the left DMPFC-left inferior temporal gyrus FC for stressful life events. For left MFG-left inferior occipital connectivity, the low parental warmth group showed a negative correlation between PRS and FC ($r = -0.3436$, $p < .0001$), and the other two groups showed no significant correlation. For left MFG-left superior frontal connectivity, the low parental warmth group showed a marginally negative correlation between PRS and FC ($r = -0.1487$, $p = .0559$), and the other two groups showed no significant correlation. For left DMPFC-left inferior temporal connectivity, the low stressful life events group showed a negative correlation between PRS and FC ($r = -0.2330$, $p = .0025$), the high stressful life events group showed a positive correlation between PRS and FC ($r = 0.2373$, $p = .0054$), and the medium groups showed no significant correlation. These results suggested that the gene effect on brain function and impulsivity was significant only in the low parental warmth or high (or low) stress group.

Discussion

The present study identified a set of genes that interacted with parental warmth or stressful life events to affect delay discounting performance. The assembled polygenic score based on genes that interacted with parental warmth was significantly correlated with a lot of functional connectivity, especially the left MFG-left inferior occipital gyrus and left MFG-left superior frontal gyrus functional connectivity; the polygenic score based on genes that interacted with more stressful life events was significantly correlated with functional connectivity between left DMPFC and several other regions. These gene–brain connectivity associations were significant when parental warmth was low or when stress level was high (or low), which is consistent with the research literature summarized in the introduction (Fields et al., 2014; Kahn et al., 2015).

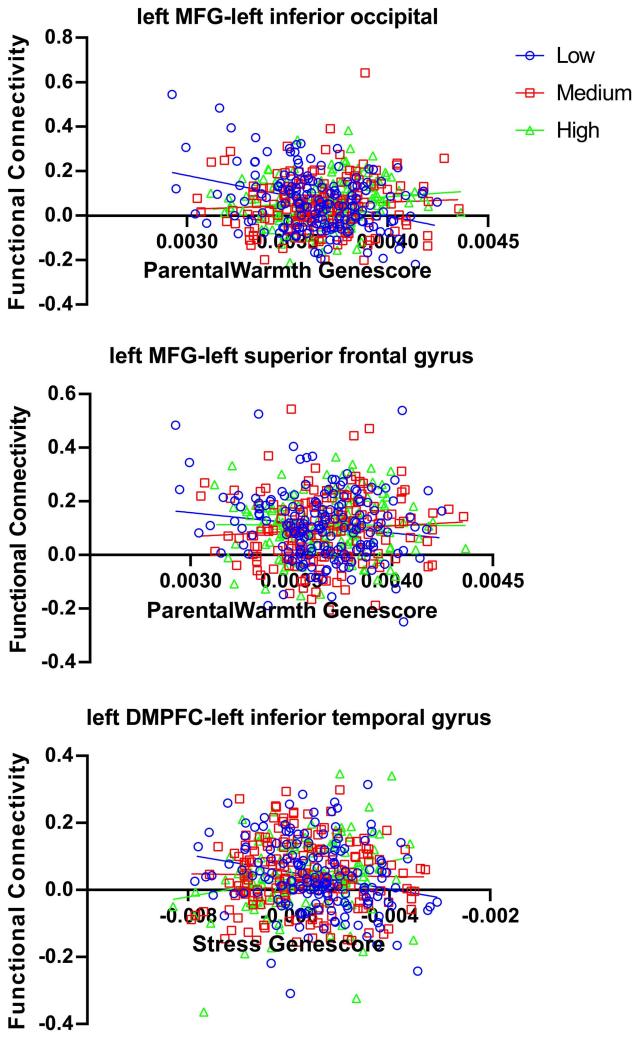
To the best of our knowledge, the present study is the first to include both protective and risk environmental factors on impulsivity. We found that protective and risk environmental factors interacted with different gene sets and these genes affected different brain networks, suggesting that protective and risk environment factors influence impulsivity through distinct biological pathways. These results deserve more attention in future studies.

We found that 14 genes significantly interacted with parental warmth and six genes interacted with stressful life events in their effects on impulsivity. Functional annotations of these genes, although still limited, suggested possible pathways through which these genes influence the neural system and contribute to impulsivity, especially under high (or low) stress or low parental warmth. CTNND2 is located on the short arm of chromosome 5 in humans, codes for δ-catenin, which is necessary for maintaining the structure and function of neurons in the cerebral cortex (Ho et al., 2000), and is expressed almost entirely in neurons (Ho et al., 2000; Matter et al., 2009). This gene has been implicated in anxiety disorder, major depressive disorder, Alzheimer's disease, autism spectrum disorder, and schizophrenia (Ho et al., 2000; Lu et al., 2016). Similarly, SLC7A14 is expressed in neural tissues and has been associated with bipolar disorder (Gonzalez et al., 2016). CACNG1–CACNG8 is a gene family coexpressed in human brains for regulating Ca^{2+} channel function (Burgess et al., 2001; R. S. Chen et al., 2007), and CACNG5 is associated with schizophrenia and bipolar disorder (Curtis et al., 2011; Guan et al., 2016). CTNNA3 plays an essential role in cellular adherence, and is associated with autism spectrum disorder and schizophrenia (Butler et al., 2015; Xu et al., 2013), as well as substance dependence, the last of which is often accompanied with impulsive behavior (Drgon et al., 2009; Liu et al., 2006; Uhl et al., 2010). Interestingly, CTNNA3 has also been found to interact with the family environment to affect cigarette smoking (Cheng et al., 2021; J. D. Smith et al., 2011). Further studies need to annotate the functions of all these genes and reveal the underlying mechanisms of gene–environment interaction (e.g., epigenetic mechanisms).

Using left MFG, and left DMPFC as seeds, we found significant associations between brain functional connectivity and gene PRSs, especially for subjects with more (or less) stressful life events or low parental warmth. All these identified brain regions have been reported in neuroimaging studies of impulsivity (Noda et al., 2020). For example, increased activity in the left lateral occipital cortex (LOC) and left MFG predicted the amount of future rewards

Figure 4

Interaction of PRS and Environmental Factors on Functional Connectivity



Note. PRS = polygenic risk score; MFG = middle frontal gyrus; DMPFC = dorsal medial prefrontal cortex. See the online article for the color version of this figure.

(Q. Wang et al., 2021). Another study showed that MFG and occipital gyrus were associated with the subjective value of delayed rewards (Prévost et al., 2010). A review of studies found that primarily the frontal gyrus and middle temporal gyrus were involved in predictions in the DD task, which were associated with value consideration (Noda et al., 2020). Furthermore, stress has been found to modulate the activation of dorsolateral prefrontal cortex and to increase the likelihood of choosing smaller immediate rewards (Aranovich et al., 2016). These results were consistent with our findings. In addition to the seed regions we selected, we found functionally connected regions mostly belonging to the δ system according to the β–δ model, which was related to the delay rewards (McClure et al., 2007). Still, there are differences in the effects of these genes on the brain. Genes interacting with the protective environmental factor mainly influenced brain connectivity of left MFG, while genes interacting with the risk environmental factor influenced brain connectivity of left DMPFC. Thus, these results suggest that under different environmental conditions, the gene effects on the brain connectivity of the δ system (evaluating delayed rewards) may change to affect individual impulsivity.

The present study suggested that stressful life events and parental warmth modulated the effect of genes on impulsivity, that is, under high (or low) stress or low parental warmth, we could find significant gene effects on impulsivity and brain functional connectivity. In fact, these environmental factors were not significantly correlated with DD performance, nor were any SNP (Supplemental Figure S1, SNP main effect without environmental information controlled). Our results suggested that future genetic and neuroimage studies should take these environmental factors into account.

Interestingly, our results showed a stronger main effect of genes in the interaction model with parental warmth compared to that with stressful life events. This could be a purely statistical issue since the significant interaction means the main effect of genes depends on the condition of the environmental factors (Figure 4). The present study thus focused on the interaction effect only. Another possible reason is parental warmth is more heritable than stressful life events. The stressful life events exposure could not be predetermined by genes, whereas parental warmth may associate with the personality of parents (de Haan et al., 2012; Truhan et al., 2022), which has shown 30%–60% heritability in twin and family studies (Sanchez-Roige, Gray, et al., 2018).

Several limitations of this study need to be mentioned. First, our GEWIS sample included 1,145 subjects, which is not a very large sample size in this field. Future studies with larger sample size can confirm our results and may also reveal the effects of other potential genes. Second, the identified brain regions differed for PRS calculated at different thresholds. This is because PRS calculated at a looser threshold may capture more genetic effects. Usually, PRS was calculated at multiple thresholds, and only the one with the best prediction was reported. We reported the results of all PRS; some could be false positive and should be further examined. Third, we tested gene–environment interaction with genotype data and associated genes to brain functional connectivity; future epigenetic studies can reveal the underlying biological mechanism. Fourth, only including healthy participants may limit the generalizability of our results to other populations.

Conclusion

To conclude, the present GEWIS identified several gene–environment interactive effects on impulsivity. We further found that the genes that interacted with parental warmth were significantly correlated with functional connectivity (especially the left MFG-left inferior occipital gyrus and left MFG-left superior frontal gyrus functional connectivity) and that the genes that interacted with more stressful life events were significantly correlated with functional connectivity of left DMPFC with other brain regions. Our findings suggest that protective and risk environmental factors can modulate genetic effects on impulsivity and their neural mechanisms. Further studies are needed to specify the underlying biochemical and neural mechanisms.

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