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Increased brain activity to unpleasant stimuli in individuals with the 7R allele of the DRD4 gene

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Abstract

The aim of the study was to examine functional brain activity in response to unpleasant images in individuals with the 7-repeat (7R) allele compared to individuals with the 4-repeat (4R) allele of the dopamine receptor D4 (*DRD4*) gene (VNTR in exon 3). Based on the response ready hypothesis, individuals with the *DRD4*-4R/7R genotype were expected to show greater functional brain activity in response to unpleasant compared to neutral stimuli in specific regions of the frontal, temporal, parietal and limbic lobes, which form the networks involved in attentional, emotional, and preparatory responses. Functional Magnetic Resonance Imaging activity was studied in 26 young adults (13 with the *DRD4*-4R/7R genotype and 13 with the *DRD4*-4R/4R genotype). Participants were asked to look at and subjectively rate unpleasant and neutral images. Results showed increased brain activity in response to unpleasant images compared to neutral images in the right temporal lobe in participants with the *DRD4*-4R/7R genotype versus participants with the *DRD4*-4R/4R genotype. The increase in right temporal lobe activity in individuals with *DRD4*-4R/7R suggests greater involvement in processing negative emotional stimuli. Intriguingly, no differences were found between the two genotypes in the subjective ratings of the images. The findings corroborate the response ready hypothesis, which suggests that individuals with the 7R allele are more responsive to negative emotional stimuli compared to individuals with the 4R allele of the *DRD4* gene.

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Keywords

Magnetic Resonance Imaging; Emotion; Attention-Deficit/Hyperactivity Disorder; Risk taking

1. Introduction

Dopamine is a key neurotransmitter, which regulates cognition, attention, emotional processing, motor activation, short-term memory, behavioral inhibition and reward (Wickens, 1990; Nieoullon, 2002; Dreber et al., 2009; Eisenberg et al., 2010b). One of the most studied genes is the dopamine receptor D4 (*DRD4*), which is located near the telomere of chromosome 11p. The *DRD4* gene has alleles due to variation in a 48 base pair tandem repeat (VNTR) in exon 3. The 48 base pair VNTR in exon 3 ranges from 2-repeat alleles (2R) to 11-repeat alleles (11R). The 4-repeat (4R) of the *DRD4* gene is the most common allele with a global mean allele frequency of 64.3% (Chang et al., 1996). The 7-repeat (7R) of the *DRD4* gene is the second most common allele with a global mean allele frequency of 20.6%, appearing with high frequency in the Americas (Chang et al., 1996). The 7R allele originated as a rare mutational event and was recently affected by positive selection (Ding et al., 2002). The 7R allele is estimated to have emerged 40,000 to 50,000 years ago, which is the same time that major human migration occurred (Wang et al., 2004). This genotype, including its homozygous and heterozygous variations, is found more frequently in populations who had to take great risks to travel long distances, such as early immigrants to the Americas (Chen et al., 1999; Eisenberg et al., 2010a). The association with risk taking was corroborated by research showing that individuals with the 7R allele of the *DRD4* gene engage in more financial risk taking compared to those without this genotype (Dreber et al., 2009).

Humans with at least one 7R allele show increased levels of physical activity (Faraone et al., 2001; Kluger et al., 2002; Grady et al., 2003; Grady et al., 2005b; Li et al., 2006; Grady et al., 2013) and appear to be more reactive to environmental factors (Sheese et al., 2007; Belsky et al., 2009; Olsson et al., 2011; Grady et al., 2013). The 7R allele is over-represented in the phenotype of Attention-Deficit/Hyperactivity Disorder (ADHD) (LaHoste et al., 1996; Faraone et al., 2001; Grady et al., 2003; Grady et al., 2005a; Li et al., 2006). In addition, the 7R allele is associated with problematic behaviors including: alcoholism (MacKillop et al., 2007), financial risk-taking (Dreber et al., 2009), disinhibition (Congdon et al., 2008), increased sexual behavior, and infidelity (Zion et al., 2006; Eisenberg et al., 2007; Garcia et al., 2010). However, 7R carriers have an advantage in some tests of reaction time (Swanson et al., 2000a; Langley et al., 2004) and executive function (Swanson et al., 2000b; Gornick et al., 2007; Johnson et al., 2008), though these results have not been consistently replicated (Barkley et al., 2006; Konrad et al., 2010). Intriguingly, a study by Grady et al. (2013) has shown that the 7R allele contributes to longevity by moderating the beneficial effects of an enriched environment in increasing lifespan. The 7R allele of the *DRD4* gene has been associated with the response ready hypothesis, which suggests that individuals with hypervigilance might be selected for by environments that are resource-depleted, time critical, or rapidly changing (Jensen et al., 1997; Wang et al., 2004). It is speculated that the 7R allele and its association with the response ready hypothesis might

have played a role in its positive selection and human migration (Chen et al., 1999; Ding et al., 2002; Wang et al., 2004; Grady et al., 2013).

The *DRD4* receptor protein is expressed in several brain regions, with high levels in the prefrontal cortex (PFC), middle temporal lobe, and limbic areas, i.e. hippocampus, amygdala, and hypothalamus (O'Malley et al., 1992; Meador-Woodruff et al., 1994; Oak et al., 2000). The human attentional network utilizes the superior parietal, inferior parietal, and superior temporal lobes for the orienting response, anterior cingulate for executive functioning, and lateral PFC for control (Fan and Posner, 2004). Previous research has shown that processing of negative emotional stimuli involves the inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus (Davidson and Irwin, 1999), right temporal lobe (Aldhafeeri et al., 2012), precuneus, inferior parietal lobules (Ferri et al., 2013), hippocampus, parahippocampus, and amygdala (Davidson and Irwin, 1999; Nolte, 2002; Aldhafeeri et al., 2012). In addition, the medial, dorsolateral, and ventrolateral PFC are involved in the appraisal process of emotional stimuli (Hariri et al., 2000; Goldin et al., 2008; Rosen and Levenson, 2009).

The aim of this study was to examine functional brain activity in response to unpleasant and neutral images in individuals with and without the 7R allele of the *DRD4* gene. Based on the response ready hypothesis, we expected that individuals with a 7R allele would show increased brain activity compared to those without a 7R allele in response to unpleasant stimuli in the bilateral PFC (inferior, middle, and superior frontal gyri), limbic areas (hippocampus, parahippocampus, and amygdala), parietal lobe (inferior parietal lobule and superior parietal lobule), and the right temporal lobe, which are involved in attention, processing of sensory information, and emotions.

2. Methods

2.1 Participants

Twenty-six participants were recruited from the Multimodal Treatment Study of ADHD (MTA) at the University of California, Irvine (UCI). The MTA sample at UCI originally consisted of 144 children (96 with ADHD and 48 normative comparison children) who were seven to nine years old when they first enrolled in 1994 to 1996. After the treatment portion of the MTA study ended, the participants were followed on a regular basis for 16 years. At the time of the present study, there were 68 participants with a diagnosis of ADHD and 41 normative comparison participants (a total of 109) that were still participating in the follow-up protocols. The MTA sample was well-defined in terms of mental health status and dopamine genotypes were available for 86 participants (Swanson et al., 2000a). All 86 young adults were contacted regarding participation in the study. Forty participants were consented for the present study of which 13 had a heterozygous 7R allele (4R/7R). Participants with the *DRD4*-4R/7R genotype were age and gender matched with 13 participants with the *DRD4*-4R/4R genotype because the *DRD4*-4R/4R is the more common genotype. Eleven participants with the *DRD4*-4R/7R genotype and seven participants with the *DRD4*-4R/4R genotype had a childhood diagnosis of ADHD. All participants abstained from drugs and alcohol use before the functional Magnetic Resonance Imaging (fMRI) scan,

which was verified with urinary and breath drug screens. Table 1 provides an overview of the participants' characteristics.

2.2 Functional Magnetic Resonance Imaging (fMRI)

Each participant underwent one fMRI scan at the Center for Functional Onco-Imaging, which is equipped with a 3.0T Philips Achieva scanner and MRI compatible visual display, auditory stimuli, and response device systems. Structural and functional MRI acquisition, quality control, and calibration methods developed by the Center were utilized for the proposed experiments.

The MRI operator ran quality assurance tests daily at the beginning of the day. Each session started with a high resolution (1 mm isotropic voxel size) T1 weighted anatomic scan using 3D MPRAGE pulse sequence with the following parameters: TR/TE = 11/3.3 ms, TI = 1100 ms, TFE = 192, number of slices = 150, SENSE factor = none, Flip angle = 180°, no SENSE acceleration was used and total acquisition duration was 7 minutes. For fMRI scans conventional T2*-weighted gradient echo planar sequences (GE-EPI) were used, with TR/TE = 2500 ms/30 ms, flip angle 90°. Fat-saturation prepulses were included to avoid fat signal overlapping the brain pixels. Slices were in the oblique-axial plane parallel with the AC-PC plane, with 4 mm thickness, and a 1 mm inter-slice gap, and acquired in ascending order. The acquisition matrix was 96×80, not interpolated, with 220 mm FOV. Typically, whole-brain coverage was achieved with 32 slices. The MRI acquisition was sequential. Responses to the task during scanning were monitored using a 4-button keypad (Current Designs, INC, Philadelphia, PA), and reaction times were recorded for subsequent psychophysical analysis of timing and accuracy of task performance. All stimuli were presented and responses recorded using Cogent 2000 software environment (Wellcome Department of Imaging Neuroscience, UK). Head movement in the scanner was restrained by vacuum pillows and tape across the subject's forehead. A precautionary screening was used to exclude participants who may have contraindications to MRI.

2.3 Emotional stimuli

Participants were asked to look at unpleasant images (e.g., images of negative emotional faces, physical injuries, and insects) and neutral images (e.g., images of neutral faces, landscapes and household items) from the International Affective Picture System (IAPS) (Lang et al., 2008) during the scan. More specifically, participants were asked to look at 24 neutral and 24 unpleasant images¹, which were presented in 8 blocks of 3 neutral images followed by 3 unpleasant images. Each image was presented for 5 seconds and was rated within those 5 seconds by participants according to neutrality and unpleasantness. The participants used a keypad with 4 buttons to indicate their rating on a scale from 1 (neutral) to 4 (extremely unpleasant). There were no rest periods between images during these relatively brief sessions. Prior to the scan, participants were familiarized with sample images from the IAPS without labeling or rating them.

¹Neutral Images: 1900,2240, 2280, 2381, 2393, 2745, 2840, 2980, 5030, 5200, 5201, 5600, 5731, 5750, 5760, 5780, 5800, 5890, 5891, 5982, 6150, 7035, 7550, 9070
Unpleasant Images: 1050, 1111, 1200, 1275,1932, 2095, 2110, 2276, 2375.1, 2688, 2700, 3181, 3030, 3301, 3550, 7380,8480, 8485, 9050, 9410, 9421, 9570, 9585, 9810

2.4 Image processing

Brain images were processed and analyzed with the Statistical Parametric Mapping software, SPM8 (Wellcome Department of Imaging Neuroscience, UK) in MATLAB 7.9 (MathWorks, Natick, MA, USA). Six motion parameters (three rotational and three translational) were used for image realignment and motion correction. Brain volume images with more than 2 mm displacement or 2° rotation were excluded. As a result, 13 out of 240 brain volumes were excluded from one male participant with the *DRD4-4R/4R* genotype. All images were motion corrected by realignment to the first image, co-registration with the anatomical scan, normalized using the Montreal Neurological Institute (MNI) brain template, and spatially smoothed with an isotropic 5 mm full-width-half-maximum Gaussian kernel.

A first-level general linear model analysis (GLM) was used to generate Blood Oxygen Level Dependent (BOLD) contrasts between unpleasant and neutral images for each participant at $p = 0.001$ and a voxel threshold of 20. A second-level analysis used the contrast images from the first-level GLM analyses in an analysis of variance (ANOVA) to compare BOLD contrasts of brain activation during unpleasant versus neutral images between the two genotypes at $p = 0.05$ (False Discovery Rate-corrected) and a voxel threshold of 20.

To provide additional information about brain activation patterns in response to unpleasant compared to neutral images for each genotype, BOLD contrasts from the first-level GLM analyses were examined with a second-level random effects model analysis at $p = 0.001$ (uncorrected) and a voxel threshold of 20. Clusters were identified by SPM8 and translated into Talairach space with Brett transformations using the MNI-Talairach Viewer (UCI - Institute for Clinical and Translational Science).

2.5 Genotyping

DNA isolation from blood samples and genotyping/sequencing of the *DRD4* VNTR was conducted as described previously (Ding et al., 2002; Grady et al., 2003; Wang et al., 2004; Grady et al., 2013).

All experiments were carried out in accordance with the Institutional Review Board at the University of California, Irvine, and were consistent with Federal Guidelines.

3. Results

3.1 Emotional ratings

A significant main effect revealed that unpleasant images were rated significantly more unpleasant than neutral images ($M = 2.72$, $S.D. = 0.69$ versus $M = 1.19$, $S.D. = 0.24$, $F(1,24) = 148.25$, $p < 0.001$). No group differences were found in the image ratings between the two genotypes (see Table 1). Therefore, the choice of stimuli was appropriate and confirmed by this main effect.

3.2 fMRI group differences

Individuals with the *DRD4-4R/7R* genotype, compared to the *DRD4-4R/4R* genotype, showed significant increased BOLD activity in the right temporal lobe in response to unpleasant versus neutral images (see Fig. 1, Table 2).

3.3 fMRI activity in the *DRD4-4R/7R* genotype

Participants with the *DRD4-4R/7R* genotype showed increased BOLD activity in response to unpleasant images compared to neutral images in the right superior frontal gyrus, right middle frontal gyrus, right middle temporal gyrus, left parahippocampal gyrus, left posterior cingulate, right cingulate, right precuneus, left cuneus, and the bilateral inferior parietal lobules, which are involved in paying attention, showing empathy, and preparing for action (see Fig. 2, Table 3).

3.4 fMRI activity in the *DRD4-4R/4R* genotype

Participants with the *DRD4-4R/4R* genotype showed increased BOLD activity in response to unpleasant images compared to neutral images, which was limited to the precuneus and cingulate gyrus in the right parietal lobe (see Fig. 2, Table 4).

4. Discussion

The findings corroborate the response ready hypothesis for the *DRD4-4R/7R* genotype at the neurobehavioral level. Individuals with the *DRD4-4R/7R* genotype showed significantly more right temporal lobe activity while viewing unpleasant images compared to those with the *DRD4-4R/4R* genotype. The right temporal lobe is primarily associated with processing of sensory and emotional information (Rosen et al., 2002; Aldhafeeri et al., 2012). Thus, the greater activation of the right temporal lobe suggests a greater involvement in processing emotional stimuli in individuals with the *DRD4-4R/7R* compared to those with the *DRD4-4R/4R* genotype.

Additional findings for each genotype revealed that individuals with the *DRD4-4R/7R* genotype showed increased brain activity in a complex network including the frontal, temporal, limbic, and parietal lobes when viewing unpleasant compared to neutral images. More specifically, participants with the *DRD4-4R/7R* genotype showed activation in the parietal cortex, cingulate, and PFC (Fan and Posner, 2004), which are associated with attention to and appraisal of emotional stimuli (Hariri et al., 2000; Goldin et al., 2008; Rosen and Levenson, 2009). As expected, both *DRD4-4R/7R* and *DRD4-4R/4R* genotypes were associated with activation of inferior parietal regions, which are involved in passive observation (Cunnington et al., 2006), but only participants with the 7R allele showed activation of DLPFC (Brodmann areas 8, 10, and 46), which reflects attention and preparation for action (Cunnington et al., 2006; Herwig et al., 2007). In addition, the activation of frontal and temporal regions in participants with the 7R allele indicates that the stimuli were perceived as meaningful (Decety et al., 1997). Furthermore, those with the 7R allele showed activation in the right middle temporal gyrus and right cingulate gyrus, which have been associated with empathy during perception of unpleasant or painful stimuli in others (Gu et al., 2010; Lang et al., 2011; Azevedo et al., 2012). In contrast, participants

with the *DRD4-4R/4R* genotype showed brain activation in response to unpleasant compared to neutral images, which was limited to the cingulate gyrus and precuneus in the right parietal lobe without involvement of limbic, frontal or temporal brain areas, suggesting a more passive processing of information.

Intriguingly, participants with the *DRD4-4R/4R* genotype rated unpleasant stimuli as unpleasant as those with the *DRD4-4R/7R* genotype although their brain activation pattern indicates less of a response. Thus, the two groups differ in their right temporal brain activity but not in their self-reported emotion. This suggests a mismatch between brain activity and subjective emotional experience. Participants with the *DRD4-4R/4R* genotype may be over-reporting their emotional experience or participants with the *DRD4-4R/7R* may be under-reporting their emotional experience.

Taken together, participants with the 7R allele showed a more global and intense activation pattern in response to unpleasant images, which may be indicating increased attention, showing empathy, and preparing for action during unpleasant stimuli. Given higher propensity for risk taking with the 7R allele of the *DRD4* gene, the results support the notion that part of risk taking is an appropriate risk assessment that includes paying close attention to unpleasant or threatening stimuli. Furthermore, risky decision-making behaviors have been associated with activation in regions of the temporal lobe including the temporoparietal junction, temporal pole, and the middle and superior temporal gyri (Rodrigo et al., 2014).

However, there are some limitations that require interpreting the findings of the present study with caution. Although not unusual for brain imaging studies, the present study had a small sample size, which may have compromised statistical power, replicability, and stability of the findings. Since pleasant stimuli were not included in this study, it is not possible to determine whether the increased brain activations reflect response readiness rather than an overwhelmed brain experiencing overload from unpleasant stimuli. Similarly, the present findings cannot distinguish between appraisal and response processes. In addition, risk-taking, attention, and empathy measures were not administered, so that the link between brain activity and risky behaviors, attention and empathy was not directly examined. However, by only investigating *DRD4-4R* homozygous individuals in comparison to *DRD4-7R* heterozygous individuals, genetic heterogeneity was minimized and our ability to detect differences in brain activity was potentially maximized. Clearly, further studies are warranted.

Despite these limitations, the present findings contribute to the concept of the *DRD4-4R/7R* genotype as a "plasticity gene" (Belsky et al., 2009). Grady et al. (2013) proposed that the 7R allele of the *DRD4* gene may mediate reactivity to environmental stimuli via a dopamine signaling deficit. The present study corroborates this hypothesis by showing that individuals with the *DRD4-4R/7R* genotype are less likely to ignore negative emotional stimuli. Such mechanisms underlying the 7R allele of the *DRD4* gene associated with a response ready hypothesis (Jensen et al., 1997) may have played a role in its positive selection and human migration (Chen et al., 1999; Ding et al., 2002; Wang et al., 2004; Grady et al., 2013).

Forty thousand to 50,000 years ago, humans may have encountered conditions leading to large migrations. Migration into new territories requires a mindset that is dominated by both risk-taking and appropriate response readiness to increase survival. Ding et al. (2002) found that the 7R allele of the *DRD4* gene is under positive selective pressure, which raises questions about its adaptability to modern culture. According to Sheese et al. (2007) the 7R allele is associated with a greater influence of parenting, which allows the caregiver more influence on the behavior of the child and increases the child's adaptation to the social environment. The 7R allele may predispose an individual to be more reactive to the environment, hence faster reaction times (Swanson et al., 2000a) and negative behavioral outcomes in an unfavorable environment (Sheese et al., 2007; Olsson et al., 2011). In particular, modern industrialized environments may increase the risk for negative behaviors in individuals with a 7R allele of the *DRD4* gene. Negative behaviors in response to modern environments in individuals with the 7R allele may include ADHD and associated conditions such as drug abuse, financial risk taking, disinhibition, and sexual infidelity (Zion et al., 2006; Eisenberg et al., 2007; MacKillop et al., 2007; Congdon et al., 2008; Dreber et al., 2009; Garcia et al., 2010; Olsson et al., 2011). Such negative behaviors may be the result of dopamine dysregulation, which is at the core of ADHD and associated conditions (Spencer et al., 2007; Swanson et al., 2007; Volkow et al., 2009; Volkow et al., 2011).

Given the documented link between the 7R allele of the *DRD4* gene and health risk behaviors, future studies should focus on the effects of health messages (e.g., health warning labels) in this genotype. Within this context, the results of the present study suggest that individuals with a *DRD4*-4R/7R genotype might be more responsive to unpleasant visual health warning labels about risky drug and sexual behaviors compared to individuals with the more common *DRD4*-4R/4R genotype. Providing health information and health warning labels in a visual fashion may be a tailored intervention to prevent and reduce health risk behaviors in individuals with the 7R allele of the *DRD4* gene.

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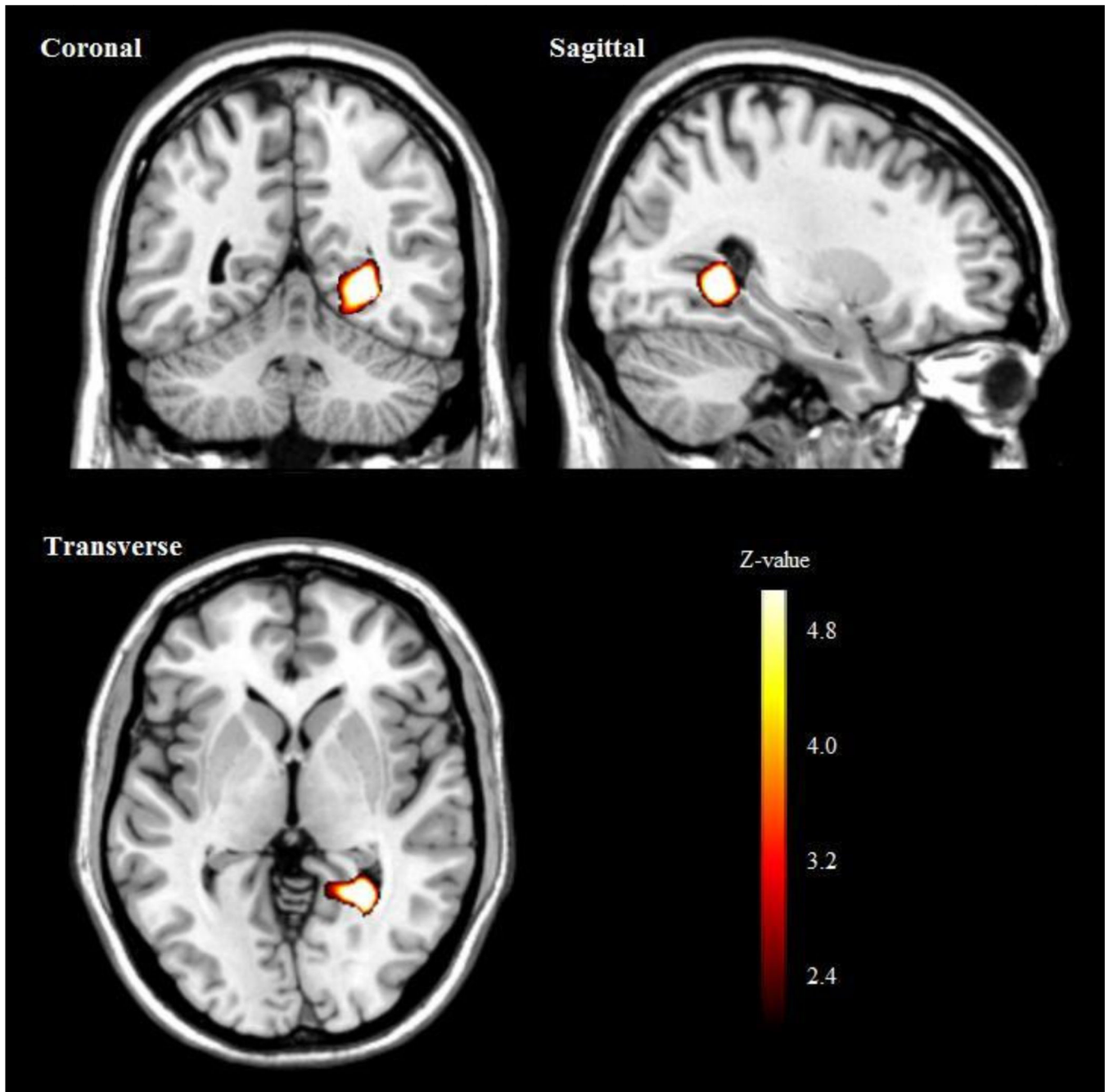


Fig. 1.
Right temporal lobe activation in response to unpleasant versus neutral images in the *DRD4-4R/7R* compared to the *DRD4-4R/4R* genotype.

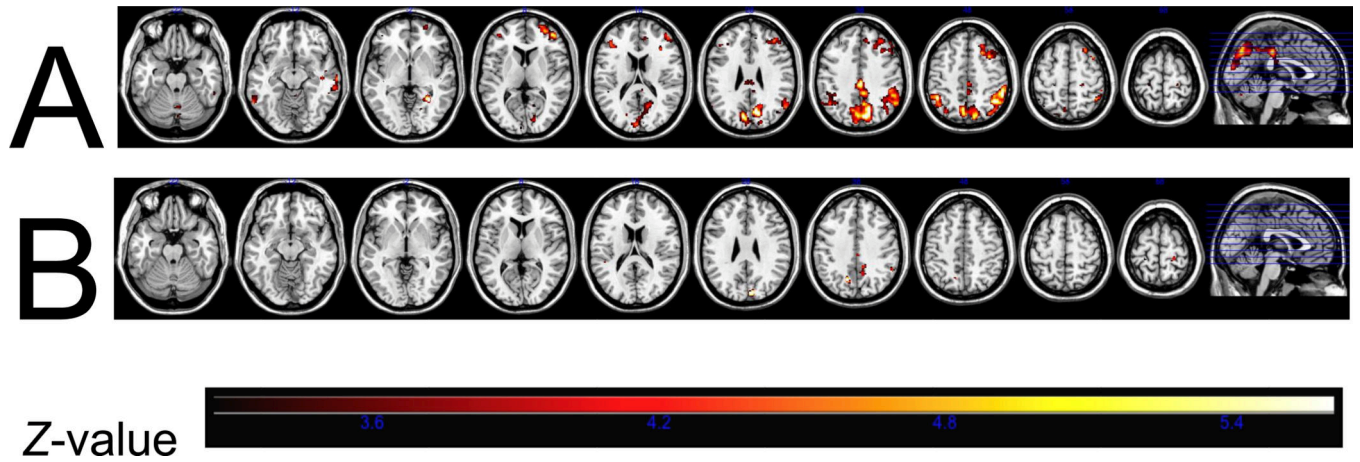


Fig. 2.
Brain activation in response to unpleasant versus neutral images in the *DRD4*-4R/7R genotype (Panel A) and the *DRD4*-4R/4R genotype (Panel B).

Table 1

Participant characteristics

	DRD4-4R/4R (<i>n</i> = 13) <i>M</i> (<i>S.D.</i>) or %	DRD4-4R/7R (<i>n</i> = 13) <i>M</i> (<i>S.D.</i>) or %	Statistics
Age, years	23.23 (1.17)	23.38 (1.66)	$t(24) = -0.27, p = 0.78$
Male	85%	85%	$\chi^2(1, N = 26) = 0.00, p = 1.00$
Female	15%	15%	$\chi^2(1, N = 26) = 0.00, p = 1.00$
Right-handed	85%	92%	$\chi^2(1, N = 26) = 0.38, p = 0.54$
Caucasian	69%	77%	$\chi^2(4, N = 26) = 4.39, p = 0.36$
Employed	69%	85%	$\chi^2(1, N = 26) = 0.87, p = 0.35$
Education, years	12.62 (0.96)	13.54 (1.45)	$t(24) = -1.91, p = 0.68$
BMI	27.06 (2.91)	24.98 (6.16)	$t(24) = 1.10, p = 0.28$
IQ	104.92 (15.03)	99.92 (13.82)	$t(24) = 0.88, p = 0.39$
Birth weight, kg	3.26 (0.54)	3.55 (0.46)	$t(24) = -1.48, p = 0.15$
Prematurity	8%	15%	$\chi^2(2, N = 26) = 2.38, p = 0.30$
ADHD in childhood	62%	85%	$\chi^2(1, N = 26) = 1.76, p = 0.19$
AHA ¹ Child Score	8.92 (6.28)	10.85 (6.45)	$t(24) = 0.77, p = 0.45$
AHA ¹ Adult Score	5.46 (4.81)	5.85 (5.38)	$t(24) = 0.44, p = 0.85$
Mothers smoked during pregnancy	8%	8%	$\chi^2(2, N = 26) = 0.38, p = 0.83$
Emotional valence rating			
Neutral Images	1.23 (0.28)	1.13 (0.18)	$t(24) = 1.13, p = 0.27$
Unpleasant Images	2.75 (0.69)	2.69 (0.73)	$t(24) = 0.21, p = 0.83$
Reaction times in seconds			
Neutral Images	1.98 (0.07)	1.96 (0.05)	$t(24) = 0.61, p = 0.55$
Unpleasant Images	2.09 (0.08)	2.09 (0.07)	$t(24) = -1.00, p = 0.92$
CES-D ² Total scores	7.31 (7.44)	7.77 (7.27)	$t(24) = -0.16, p = 0.87$

¹Assessment for Hyperactivity and Attention,²Center for Epidemiologic Studies Depression Scale

Table 2*DRD4-4R/7R* genotype activation versus *DRD4-4R/4R* genotype activation

Region	Side	Cluster size	BA	MINI Coordinates			F_{max}	P
				X	Y	Z		
Temporal Lobe								
Sub-gyral	R	30		28	-52	0	4.51	0.0001

Table 3

DRD4-4R/TR genotype activation

Region	Side	Cluster size	BA	MINI Coordinates			T _{max}	P
				X	Y	Z		
Frontal Lobe								
Superior Frontal Gyrus	R	920		30	40	34	5.37	0.0001
Superior Frontal Gyrus	R		8	24	24	56	5.31	0.0001
Middle Frontal Gyrus	R	462	46	46	46	12	5.81	0.0001
Middle Frontal Gyrus	R			32	52	8	4.92	0.0001
Superior Frontal Gyrus	R		10	26	58	4	4.79	0.0001
Temporal Lobe								
Sub-Gyral	R	128		28	-52	0	8.19	0.0001
Middle Temporal Gyrus	R	125	21	66	-20	-14	5.16	0.0001
Middle Temporal Gyrus	R			62	-34	-14	4.99	0.0001
Limbic Lobe								
Parahippocampal Gyrus	L	24		-34	-48	-10	6.46	0.0001
Sub-Gyral	L			-30	-54	-6	5.39	0.0001
Posterior Cingulate	L	24	31	-18	-66	12	5.81	0.0001
Lingual Gyrus	L			-18	-64	2	4.72	0.0001
Parietal Lobe								
Precuneus	R	3335		12	-72	34	7.5	0.0001
Cuneus	L			-10	-78	30	6.09	0.0001
Cingulate	R			2	-28	40	6.01	0.0001
Inferior Parietal Lobule	R	1653	40	54	-44	50	6.3	0.0001
Inferior Parietal Lobule	R		40	42	-54	48	6.1	0.0001
Inferior Parietal Lobule	R			56	-32	46	5.11	0.0001
Inferior Parietal Lobule	L	549	40	-46	-50	50	6.01	0.0001
Inferior Parietal Lobule	L		40	-44	-60	52	4.97	0.0001
Inferior Parietal Lobule	L			-54	-48	48	4.62	0.0001

Table 4*DRD4*-4R/4R genotype activation

Region	Side	Cluster size	BA	MNI Coordinates			T_{\max}	P
				X	Y	Z		
Parietal Lobe								
Precuneus	R	121		10	-52	34	4.97	0.0001
Cingulate Gyrus	R		7	14	-44	40	4.11	0.0001
Precuneus	R			12	-58	42	3.75	0.0001