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The polymorphism of dopamine D2 receptor TaqIA gene is associated with brain response to drug cues in male heroin-dependent individuals during methadone maintenance treatment

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ABSTRACT

Background: Polymorphism of the dopamine D2 receptor TaqIA gene is related to reward response, relapse risks and effect of therapy for drug addiction. Whether the cue-induced craving and brain response was related to dopamine D2 receptor TaqIA gene is unknown.

Methods: Forty-nine male heroin-dependent individuals [31 with A1 allele of the TaqIA (A1+), 18 A2 allele carriers (A1−)] under methadone maintenance treatment and 20 healthy control subjects performed a heroin cue-reactivity task during functional magnetic resonance imaging. Cue-elicited craving was measured. Difference in cue induced craving and brain response were analyzed among the three groups. Correlation analyses between craving and differential brain response, heroin use and treatment history were performed within A1+ and A1− group respectively.

Results: Compared with A1− group, A1+ group showed greater cue-induced response in the ventrolateral prefrontal cortex, medial orbitofrontal gyrus, dorsomedial prefrontal cortex, pallidum, putamen, thalamus, superior parietal lobule and superior occipital gyrus. No difference in craving was found. The response in right thalamus positively correlated with daily heroin and methadone dose in A1+ group. For A1− group, response in left ventral orbitofrontal cortex, medial orbitofrontal gyrus, ventral anterior cingulate cortex, caudate, precuneus, calcarine and bilateral pallidum negatively correlated with duration of heroin use. The response in left ventral orbitofrontal cortex, medial orbitofrontal gyrus, bilateral calcarine and right cerebellum negatively correlated with duration of methadone maintenance treatment in A1− group.

Conclusions: The findings supported that A1 allele of the TaqIA is associated with higher salience allocation to heroin-related cues in heroin-dependent patients.

1. Introduction

Drug addiction is a major public health and social issue. Genetic, environmental and drug-induced factors play a role in this chronic brain disease (Kreek et al., 2012). The estimated heritability accounted for 60% (Uhl et al., 1993). Numerous genetic association studies of drug addiction have focused on the TaqIA polymorphism (Lawford et al., 2000; Ponce et al., 2016; Richter et al., 2017, 2013), which is a common single nucleotide polymorphism (SNP, rs1800497) located in the ankyrin repeat and kinase domain containing 1 (ANKK1) 10 kb downstream from the dopamine D2 receptor (DRD2) gene. The DRD2 TaqIA polymorphism is associated with dopamine D2 receptor density which plays an important role in the context of reward. The A1 allele carriers (A1+: A1/A1 and A1/A2) of the TaqIA, compared to A2 homozygotes (A1−: A2/A2), show fewer DRD2 availability in the striatum (Eisenstein et al., 2016; Pohjalainen et al., 1998). Low level of brain DRD2 can trigger drug-seeking behavior and lead to opiate reward effects (Volkow et al., 2001). Since persons who carry the A1

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allele show a reduced sensitivity to reward, they feel the increased urge to consume substances of abuse stimulating the dopamine (DA) system (Blum et al., 2000, 2017). Individuals with A1 allele significantly increased opioid dependence risk than patients without the A1 allele (Deng et al., 2015). The A1 allele has been associated with a higher heroin consumption and poor response to methadone treatment (Lawford et al., 2000). A1 allele carriers were more likely to be heroin addicts than individuals without A1 allele (Hou and Li, 2009). Thus, the A1 allele may be a risk factor for heorin addiction. Although the two phenotypes of DRD2 TaqIA gene have been showed differences in addictive susceptibility and treatment sensitivity based on above epidemiological studies, the underlying neural basis is not clear.

Positron emission tomography (PET) studies showed reduced striatal dopamine DRD2 availability and presynaptic dopamine release in heroin-dependent subjects compared with healthy controls (Martinez et al., 2012; Zijlstra et al., 2008). Previously, combining functional magnetic resonance imaging (fMRI) and a drug cue-reactivity task, the researchers and our team demonstrated abnormal patterns of subjective response and high brain reactivity in heroin-dependent individuals, including prefrontal, mesolimbic system, visuospatial-attention regions such as dorsomedial prefrontal cortex (DMPFC), dorsolateral frontal cortex (DLPFC), ventrolateral prefrontal cortex (VlPFC), medial orbitofrontal gyrus (MOFC), ventral orbitofrontal gyrus (VOFC), ventral anterior cingulate cortex (VACC), nucleus accumbens (NAc), hippocampus, caudate, superior parietal lobule (SPL), superior occipital gyrus (SOG), as well as cerebellum (Daglish et al., 2001; Di Simplicio et al., 2012; Langleben et al., 2008; Li et al., 2015, 2013; Zijlstra et al., 2009). However, whether the abnormalities in cue-induced brain response are related to the polymorphism of TaqIA gene is unknown.

To investigate the relationship between polymorphism of TaqIA and the drug cue-induced brain response, we analyzed the brain response of heroin addicts with different allele of TaqIA during the presentation of heroin-related cues. We hypothesized that brain reactivity when exposed to heroin-related cues might be different between group with A1 allele (A1 +) and group without A1 allele (A1 −). Specifically, the A1 + patients show more intense brain activation in prefrontal, mesolimbic system and visuospatial-attention related regions relative to A1 − patients.

2. Methods

2.1. Study sample

All aspects of the study protocol were reviewed and approved by the ethics committee of Tangdu Hospital. All participants provided written informed consent to participate in this study. Participants included heroin-dependent patients under methadone maintenance treatment (MMT) and healthy control individuals. The heroin-dependent patients were recruited from Baqiao MMT clinic, Xi'an, China. All of the subjects were male smokers. Inclusion criteria for heroin-dependent patients were (1) DSM-IV-TR criteria for heroin addiction for at least 1 year; (2) being under a stable dose MMT for at least 1 month; and (3) being right-handed. Exclusion criteria for all of the subjects were (1) use of cocaine or other illegal drug use except for heroin; (2) current or past psychiatric illness other than heroin and nicotine dependence; (3) neurological signs and/or history of neurological disease; (4) history of head trauma; (5) history of cardiovascular or endocrine disease; (6) current medical illness or recent medicine use; (7) presence of magnetically active objects in the body; and (8) claustrophobia or any other medical condition that would preclude the patient from lying in the MRI scanner for approximately 40 min. The Beck Depression Inventory II (BDI) (Beck et al., 1996) and Hamilton Anxiety Scale (HAMA) (Hamilton, 1959) were applied to assess the severity of depression and anxiety symptoms, respectively.

2.2. Design and procedure

All participants were required to abstain from alcohol, tea, caffeine and any other drug or medicine 12 h before the time of MRI scan. We utilized a previously established event-related fMRI design in this study (Di Simplicio et al., 2012; Li et al., 2015, 2013; Wang et al., 2011). There were 48 trials in all, consisting of 24 heroin-related cues and 24 neutral cues. The heroin-related cues included pictures of heroin injection or paraphernalia, and the neutral cues included pictures of household objects or transportation tools. All of the cues were presented in a pseudorandomized order with E-Prime 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Picture cues were presented for 2 s with a variable 4–12 s inter-stimulus interval (mean = 8 s), during which a white cross hair with black background was displayed. The task began with a 10 s dummy scan followed by the first cue (heroin-related or neutral cue) and experimental scanning. The total task lasted for 8 min 10 s.

For heroin-dependent subjects, subjective heroin craving was evaluated by a 0–10 visual analogue scale (Di Simplicio et al., 2012) using the question, "To what extent do you feel the urge to use heroin?" (10 for the strongest craving and 0 for the least craving). Craving ratings were acquired before and shortly after each fMRI scan.

2.3. Genotyping

All heroin-dependent patients provided saliva from which epithelial cells were collected and DNA was extracted. The heroin-dependent patients were genotyped for the TaqIA (rs1800497) polymorphism (A1/A2; T/C) by the China branch of the American Applied Biosystems using pyrosequencing, and a predesigned TaqMan SNP genotyping assay. The heroin-dependent patients were categorized as A1 allele carriers (A1 +) or A2 allele homozygotes (A1 −). A1 carriers (A1 + : A1/A1 and A1/A2) were grouped together for all subsequent analyses and compared to those with A2 homozygotes (A1 − : A2/A2), same as in previous behavioral and imaging studies (Richter et al., 2013). Our objective was to explore the difference in effect of A1 + and A1 − gene types on the drug cue induced brain response in heroin-dependent individuals, just letting healthy controls be baseline. Therefore, the healthy controls were not genotyped.

2.4. MRI data acquisition

All imaging data were acquired on a 3 T MRI scanner (GE Signa Excite HD, Milwaukee, WI, USA). For fMRI images, single-shot gradient-echo echo-planar imaging was used to acquire 240 T2*-weighted image volumes. For each brain volume, 32 axial slices covering the whole brain were acquired with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, matrix = 64 × 64, field of view (FOV) = 256 × 256 mm^2, slice thickness = 4 mm, gap = 0 mm, spatial resolution = 4 × 4 × 4 mm^3. For structure images, a 166-slice high-resolution fast spoiled gradient-echo 3D T1-weighted image was also acquired with the following parameters: TR = 7.8 ms, TE = 3.0 ms, matrix = 256 × 256, FOV = 256 × 256 mm^2, slice thickness = 1 mm, spatial resolution = 1 × 1 × 1 mm^3. The structural data were carefully checked by an experienced radiologist to assure that there were no structural abnormalities.

2.5. Data analysis

The group differences in demographic information, clinical profile measures were analyzed by one-way analyses of covariance (ANOVA). The difference in duration and dose of heroin and methadone use between A1 + and A1 − group were analyzed by independent sample *t*-test. A significance threshold was set at $P < 0.05$. The fMRI data analysis was conducted with SPM8 (http://www.fil.ion.ucl.ac.uk/spm)

and DPABI (http://rfmri.org/dpabi) software. The fMRI images were slice-time corrected, motion corrected and then normalized to a standard SPM T1 template, interpolated to 3-mm isotropic voxels and spatially smoothed (Gaussian kernel of 8 mm full width at half maximum). Subjects with excessive head motion (more than 1.5 mm in translation or 1.5° in rotation) were excluded from the analysis. A statistical model for each subject was computed by applying a canonical response function. The critical contrast of interest was the heroin-related > neutral cues contrast which would reveal brain response related to the processing of heroin-related cues (Franklin et al., 2007). Differences in heroin-related cue induced brain response were analyzed with one way ANOVA at the whole-brain level among the A1+, A1− and HC group at single voxel-level threshold of $P < 0.001$. To correct multiple comparison among the above three groups, we performed Monte Carlo stimulation (Cox, 1996) at the cluster threshold of $P < 0.05$, by which the minimum 114 contiguous voxels of cluster was determined. The activation intensity of differential brain regions were extracted, and post hoc test was conducted with method of Student-Newman-Keuls (SNK) by GraphPad Prism software (https://www.graphpad.com/scientific-software/prism). Then, we chose each differential cluster observed between heroin-dependent (A1+ or A1− group) and healthy control groups segmented using Automatic Anatomy Labeling (AAL) template as region of interest (ROI). The raw data within the ROIs of the A1+ and A- group were extracted. Pearson correlation analysis was conducted between change in signal within the ROIs and craving change, heroin use history and MMT history within the A1+ and A1− group respectively.

3. Results

3.1. Sample characteristics

Fifty-three men with heroin dependence participants and 20 male healthy controls (HC group) were recruited in our study. Data from 4 patients with heroin dependence were discarded owing to excessive head motion. Of the remaining 49 patients, 31 patients who carried one or two copies of the A1 allele were designated as the A1+ group, the remaining 18 A2 allele carriers were designated as the A1− group. ANOVA analyses showed no significant differences in age, years of education and daily smoking amount among the three groups. Independent sample *t*-test indicated the A1+ and A1− group did not differ in lifetime heroin use, duration and of dosage of MMT (Table 1).

3.2. Craving

For the A1+ group, the subjective craving scores before and after cue exposure and change in craving were 1.6 ± 1.8, 2.1 ± 2.1 and 0.5 ± 1.6, respectively. For the A- group, the subjective craving scores before and after cue exposure and change in craving were 1.3 ± 0.8, 1.6 ± 1.6 and 0.1 ± 1.5, respectively. No significant difference in the craving score before cue exposure ($t = -0.89$, $P = 0.38$), after cue exposure ($t = -0.83$, $P = 0.41$) and craving change ($t = -0.88$, $P = 0.39$) was found between the two groups. No significant change in the craving score before and after cue exposure was found for the A1+ or A1− group, respectively ($t = -0.87$, $P = 0.39$; $t = -0.72$, $P = 0.47$).

3.3. fMRI results

ANOVA analysis of three groups demonstrated significantly different brain response during the processing of heroin-related > neutral cues in the prefrontal regions (right VlPFC, left DMPFC, VOFC and bilateral MOFC, VACC), mesolimbic system (right hippocampus,

Table 2
Difference in response to heroin-related > neutral cues among A+, A- and HC groups.

Brain regions		Brodmann area	Peak location			Peak *F*-value	Voxels
			x	y	z		
VlPFC	R	44	51	12	30	16.79	79
DMPFC	L	8	−18	30	51	13.90	59
VOFC	L	11	−12	15	−21	13.69	10
MOFC	L	11	−15	18	−21	17.60	24
MOFC	R	11	18	21	−18	16.69	26
VACC	L	25	−3	15	−15	13.49	27
VACC	R	25	6	21	−12	10.08	15
Hippocampus	R	NA	18	−33	0	14.24	37
ParaHippocampal	R	NA	18	−27	−12	12.38	22
Caudate	L	NA	−9	12	−6	12.64	64
Caudate	R	NA	18	18	9	13.55	84
Pallidum	L	NA	−15	6	3	18.26	45
Pallidum	R	NA	27	−12	−3	14.29	34
Putamen	L	NA	−25	3	3	15.90	154
Putamen	R	NA	27	−6	3	14.62	101
Thalamus	L	NA	−3	−15	0	18.23	138
Thalamus	R	NA	15	−15	0	18.29	147
SPL	L	7	−27	−75	48	11.59	64
SOG	L	19	−24	−81	42	11.12	16
Precuneus	L	23	−3	−54	12	10.00	33
Precuneus	R	23	3	−63	21	10.18	12
Calcarine	L	17	0	−69	15	10.27	24
Calcarine	R	17	3	−69	12	10.34	18
Cerebelum	R	NA	12	−78	−15	12.80	70

VlPFC = ventrolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, VOFC = ventral orbitofrontal cortex, MOFC = medial orbitofrontal gyrus, VACC = ventral anterior cingulate cortex, SPL = superior parietal lobule, SOG = superior occipital gyrus, NA = not applicable; R = right, L = left. NA = not applicable.

Table 1
Demographic and clinical characteristics of participants.

Characteristics	A1+ (n = 31)	A1− (n = 18)	HC (n = 20)	Group differences	
Years	35.4 ± 7.3	33.8 ± 8.2	35.2 ± 7.0	$F = 0.28$	$P = 0.75$
Years of education	9.2 ± 1.8	9.4 ± 3.4	10.0 ± 2.3	$F = 0.60$	$P = 0.55$
Cigarettes (per day)	20.5 ± 8.9	15.7 ± 8.7	13.7 ± 4.9	$F = 2.63$	$P = 0.08$
BDI scores	8.4 ± 7.4	12.5 ± 9.6	3.1 ± 4.4	$F = 7.04$	$P = 0.02$[a]
HAMA scores	8.4 ± 8.1	10.7 ± 12.7	2.9 ± 3.9	$F = 4.18$	$P = 0.00$[b]
Duration of heroin use (months)	80.1 ± 76.6	61.9 ± 60.1	NA	$t = -0.86$	$P = 0.40$
Average heroin dose (g/day)	0.5 ± 0.3	0.3 ± 0.2	NA	$t = -1.21$	$P = 0.23$
Total heroin dose (g)	1284.1 ± 1634.8	758.5 ± 1099.9	NA	$t = -1.07$	$P = 0.29$
Duration of MMT (months)	19.7 ± 14.7	20.2 ± 15.5	NA	$t = 0.10$	$P = 0.92$
Average methadone dose (mg/day)	42.7 ± 14.0	45.2 ± 13.3	NA	$t = 0.59$	$P = 0.56$
Total methadone dose (mg)	24935.9 ± 1807.3	30481.7 ± 24679.4	NA	$t = 0.97$	$P = 0.34$

[a] HC < A1+, HC < A1−, $P < 0.05$; A1+ versus A1−, no significant difference.
[b] HC < A1+, $P < 0.05$; HC versus A1−, no significant difference; A1+ versus A1−, no significant difference. NA = not applicable. The total and average heroin dose was self-reported by heroin-dependent individuals.

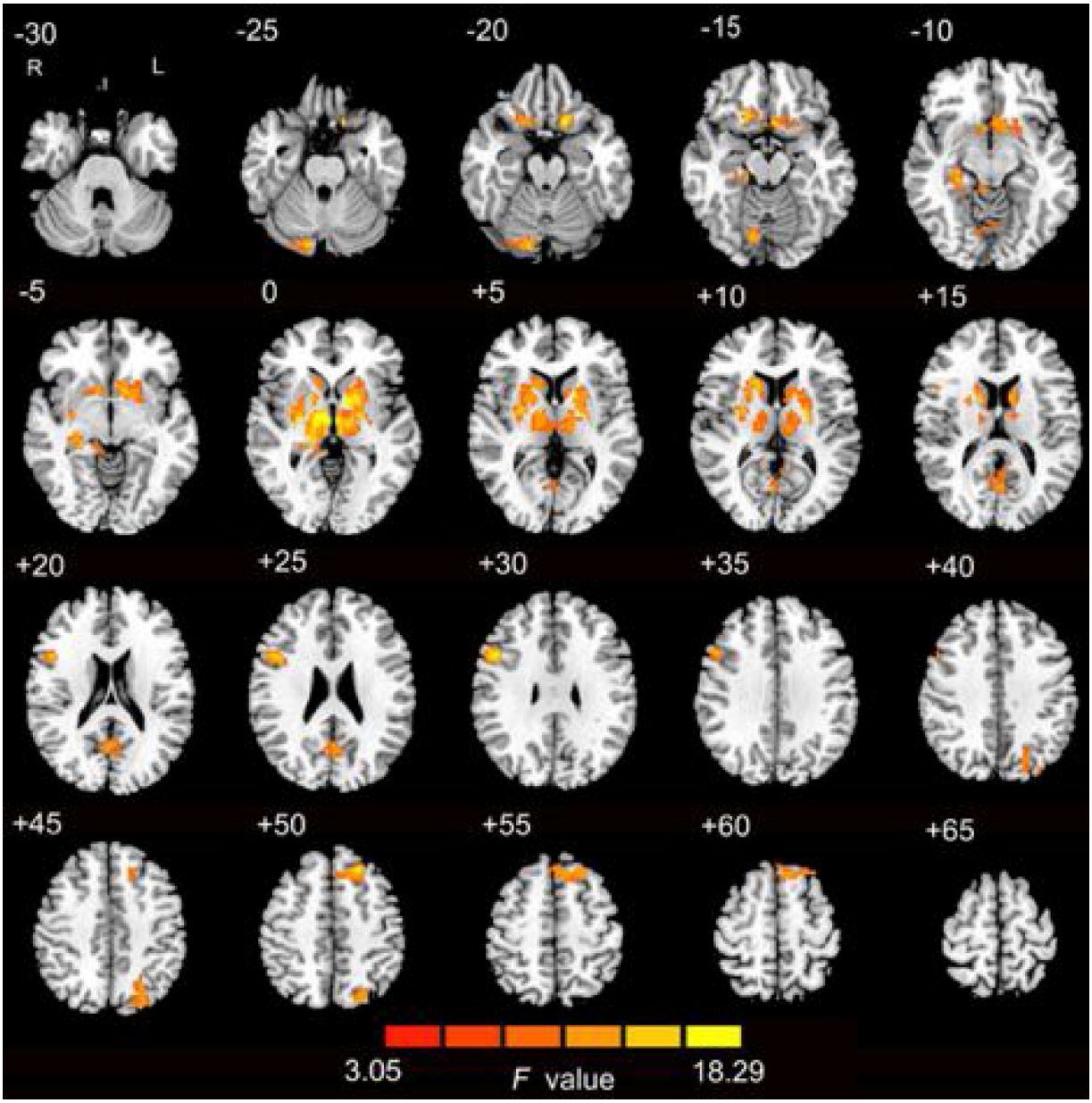

Fig. 1. Regions showing group differences in heroin-related cue induced brain response among A1+, A1− and HC groups.The threshold was corrected for multiple comparisons with Monte Carlo simulations (L = left; R = right).

parahippocampus and bilateral caudate, pallidum, putamen, thalamus), visuospatial-attention regions (left SPL, SOG and bilateral precuneus, calcarine) and right cerebellum. (Table 2, Fig. 1). Compared with HC group, the A1+ and A1− groups showed higher heroin cue induced brain response in the prefrontal regions (right VlPFC, left DMPFC, VOFC and bilateral MOFC, VACC), mesolimbic system (right hippocampus, parahippocampus, left pallidum and bilateral caudate, putamen), visuospatial-attention regions (left SPL and bilateral precuneus, calcarine) and right cerebellum (Supplementary Fig. S1). Meanwhile, A1+ group showed higher heroin cue induced brain response relative to A1− group in the right VLPFC and MOFC, left DMPFC, right pallidum and putamen, bilateral thalamus, left SPL and SOG (Fig. 2). There was no higher brain response for HC group relative to either A1+ or A1− group during exposure of heroin-related cues.

3.4. Correlation results

The heroin-related cue induced activation in right thalamus was separately positively correlated with daily heroin and methadone dose for A1+ group, but not for A1− group (heroin: $r = 0.40$, $P = 0.03$; methadone: $r = 0.43$, $P = 0.02$) (Supplementary Table S1, Fig. 3). As for A1− group, the heroin-related cue induced activation in left VOFC ($r = -0.58$, $P = 0.01$), MOFC ($r = -0.53$, $P = 0.03$), VACC ($r = -0.56$, $P = 0.02$), caudate ($r = -0.51$, $P = 0.03$), precuneus ($r = -0.56$, $P = 0.02$), calcarine ($r = -0.56$, $P = 0.02$), left pallidum ($r = -0.50$, $P = 0.03$) and right pallidum ($r = -0.54$, $P = 0.02$) were separately negatively correlated with duration of heroin use. Meanwhile, the heroin-related cue induced activation in left VOFC ($r = -0.53$, $P = 0.02$), MOFC ($r = -0.59$, $P = 0.01$), left calcarine ($r = -0.52$, $P = 0.03$), right calcarine ($r = -0.58$, $P = 0.01$) and right cerebellum ($r = -0.65$, $P < 0.001$) were separately negatively correlated with duration of MMT for A1− group, but not for A1+ group. (Supplementary Table S2, Fig. 4) No significant correlations were found between heroin-related cue induced brain activation and changes in craving within the A1− group or A1+ group. (Supplementary Table S3).

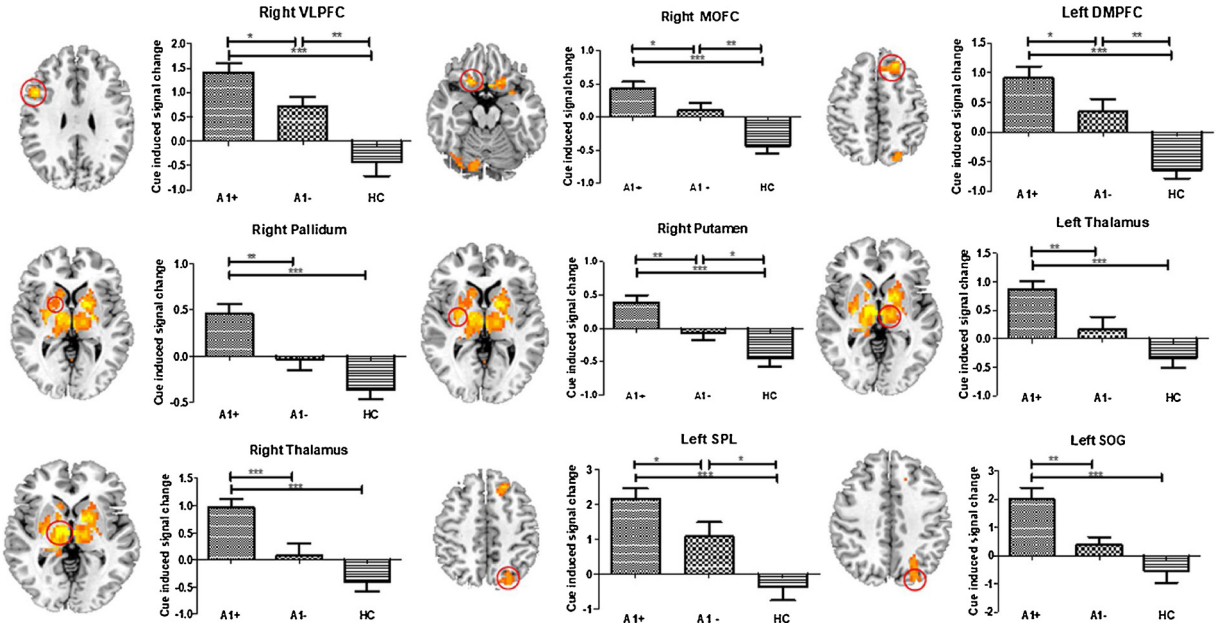

Fig. 2. Brain regions that A1 + group showed higher heroin-related cue induced brain response relative to A − group. (HC = healthy control, VLPFC = ventrolateral prefrontal cortex, MOFC = medial orbitofrontal gyrus, DMPFC = dorsomedial prefrontal cortex, SPL = superior parietal lobule, SOG = superior occipital gyrus. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.).

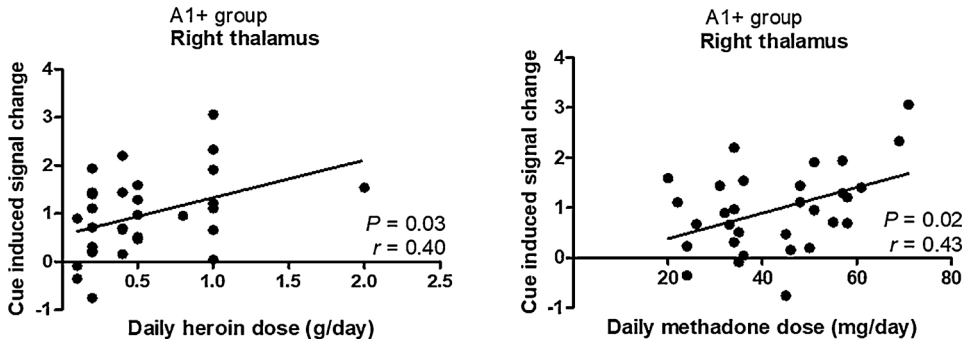

Fig. 3. Correlation map between daily heroin and methadone dose and signal amplitude of right thalamus in response to heroin-related cues in A1 + group (r = correlation coefficient; P = P-value).

4. Discussion

To the best of our knowledge, this is the first neuroimaging study to assess brain response to heroin-related cues in terms of the DRD2 TaqIA polymorphism in heroin addiction. Our findings are consistent with our hypotheses and revealed that, compared with heroin dependent individuals without A1 allele, those with A1 allele showed higher drug cue induced brain response in prefrontal, mesolimbic system and visuospatial-attention related regions.

Compared with HC group, Group A1 + and A1 − commonly demonstrated significantly greater brain response during the processing of heroin-related cues in the prefrontal regions (right VlPFC, left DMPFC, VOFC and bilateral MOFC, VACC), mesolimbic system (right hippocampus, parahippocampus, left pallidum and bilateral caudate, putamen), visuospatial-attention regions (left SPL and bilateral precuneus, calcarine) and right cerebellum. These results were in line with our previous research (Li et al., 2015, 2012; Li et al., 2013; Wang et al., 2011, 2014) and others' studies (Di Simplicio et al., 2012; Langleben et al., 2014; Walter et al., 2015) showing an enhanced cue-induced brain response in these areas. The findings demonstrated that heroin-related cues can induce enhanced salience attribution in the heroin-dependent individuals.

More importantly, compared with the A1 − group, the A1 + group demonstrated significantly higher brain response to heroin-related > neutral cues in prefrontal regions (right VLPFC, MOFC and left DMPFC), mesolimbic regions (right pallidum, putamen and bilateral thalamus), and visuospatial attention regions (left SPL and SOG).

The right VLPFC has been reported to play a role in response inhibition (Filbey et al., 2012). Heavy drinking adults with the risk allele for alcohol dependence demonstrated abnormal activation in the right VLPFC during a GO/NOGO task (Filbey et al., 2012). The VLPFC has also been reported to be associated with the flexible adaptation of behavior. A study showed that A1 + group had better task conversion flexibility than the A1 − group, indicating that A1 + group had a lower addictive threshold (Stelzel et al., 2010). The MOFC is related to monitoring the reward value (Kringelbach and Rolls, 2004). The DMPFC is implicated in decision-making, emotional information processing and goal-directed action planning (Rushworth et al., 2004). The higher drug cue induced brain activation of VLPFC, MOFC and DMPFC in A1 + group relative to A1 − group may suggest that the executive function of A1 + group be more affected relative to A1 − group.

The putamen, pallidum and thalamus are involved in mesocorticolimbic circuitry (Gu et al., 2010), which are the main distribution regions of DRD2 receptors, and are related to the craving (Sinha, 2013). The mesolimbic system has been associated with dopaminergic modulation of reward and goal-directed behavior (Goto and Grace, 2005).

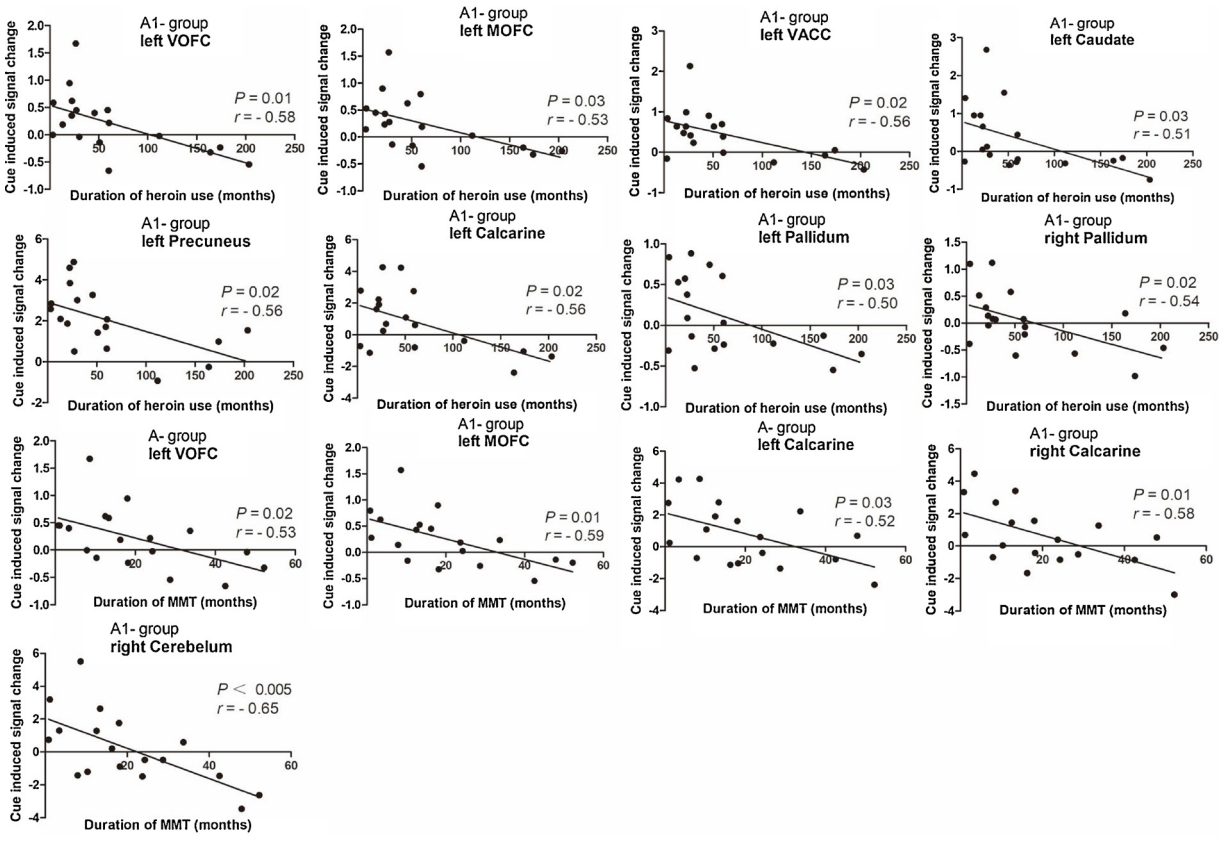

Fig. 4. Correlation maps between heroin use and Methadone maintenance treatment (MMT) history and heroin-related cue induce brain response that differed between heroin-dependent (A1 + or A1 −) and healthy control groups within the A1 − group.
(VOFC = ventral orbitofrontal gyrus, MOFC = medial orbitofrontal gyrus, VACC = ventral anterior cingulate cortex, r = correlation coefficient; P = P-value).

DRD2 TaqIA modulates DRD2 density such that carriers of the A1 allele (A1 +) have a 30% reduced DRD2 density compared to homozygous A2 allele carriers (Ritchie and Noble, 2003). This effect is particularly prominent in the striatum, such as the caudate and putamen in particular (Ritchie and Noble, 2003). The thalamus is a part of the cortico-striato-thalamo-cortical circuits underlying both reward and motivated behavior (Haber and Knutson, 2010) and cognitive control processes (Xu et al., 2017). Animal study found that greater thalamic neuronal activation was correlated with more cocaine-seeking behavior after reinstatement following a drug cue, but not after the reinstatement of behavior conditioned to a palatable food reward (Matzeu et al., 2017), suggesting that the degree of neuronal activation within the thalamic is behaviorally relevant. Together with the positive correlation between drug-related response in the right thalamus and daily heroin dose and methadone dose, the higher drug-related response of the mesolimbic regions may suggest that the reward, motivation and cognitive control be more impaired in A1 + group relative to A1 − group.

The SPL and SOG are involved in visuospatial-attention regions, which may play a role in processing the salient visual drug-related stimuli (Hahn et al., 2007). The higher heroin cue induced response in SPL and SOG in A1 + group relative to A1 − group may suggest that A1 + group be characterized by higher salient value to drug-related cue than A1 − group.

No difference in subjective craving was found between A1 + and A1 − group. However, there is also a study demonstrating that response to drug-related cues that occur before craving rather than subjective craving itself may have better predictive value in terms of relapse (Tiffany and Carter, 1998).

Interestingly, A1 − groups demonstrated negative correlation between duration of heroin use and heroin-related cue induced brain response in left VOFC, MOFC, VACC, caudate, precuneus, calcarine, and bilateral pallidum. These negative correlations of A1 − group indicated a trend of heroin-related cue induced brain response towards healthy controls, further indirectly suggested A1 + group be featured by higher salience attribution to heroin-related cues. A1 − groups also demonstrated negative correlation between duration of MMT and heroin-related cue induced brain response in left VOFC, MOFC, bilateral calcarine and right cerebellum. These negative correlations might suggest that A1 − group is sensitive to MMT. In addition, our previous study (Wang et al., 2014) showed that the drug-related BOLD signal intensity in the bilateral caudate in heroin addicts was negatively correlated with MMT duration.

Some caveats apply to this study. First, because our focus was to investigate the difference in heroin-related cue induced responses between different TaqIA genotypes of heroin-dependent individuals, the HC group was not genotyped. The healthy controls were just used as baseline. In this study, either A1 + or A1 − group commonly showed higher drug cue induced brain response in many regions when compared with HC group, which is in line with our previous research (Li et al., 2015, 2012; Li et al., 2013; Wang et al., 2011, 2014) and others' studies (Di Simplicio et al., 2012; Langleben et al., 2014; Walter et al., 2015) showing the reliability of the heroin cue-reactivity task. Second, due to the difficulty of data collection for females in the district where we recruited the subjects, we had to restrict the experimental sample to males. Therefore, whether our findings generalize to female addicts awaits further investigation. Finally, these heroin-dependent patients were under long-term MMT focused on relapse prevention and had a stable dose of methadone treatment, which has an effect on heroin cue-induced craving (Fareed et al., 2011). MMT might hindered the correlation between fMRI data and craving.

In summary, our findings suggested that the TaqIA genetic variants would influence the activation of prefrontal, mesolimbic and

visuospatial-attention related regions in response to visual drug-related stimuli among heroin-dependent individuals. Previous studies have shown that disrupted prefrontal control and hyperactive mesolimbic responses in drug cues may predict relapse risk (Sinha, 2013). A1 allele might serve as an indicator of relapse potential, although relapse behavior was not measured in this study. We suggest that future therapies for heroin addiction should pay mopplre attention to those patients with A1 allele of TaqIA genotype.

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Contributors

All authors made substantial contributions to this manuscript and take responsibility for its content. WW and YW was responsible for the study design. JC, FH, YL, XW, JZ, JL, JY and HS contributed to the acquisition of fMRI and demographical data. YL and QL performed the data analysis. WL and JC assisted with data analysis and interpretation of findings. YL drafted the manuscript. QL provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

Conflict of interest

Nothing declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.01.028.

References

Beck, A.T., Steer, R.A., Ball, R., Ranieri, W., 1996. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. J. Pers. Assess. 67, 588–597.
Blum, K., Braverman, E.R., Holder, J.M., Lubar, J.F., Monastra, V.J., Miller, D., Lubar, J.O., Chen, T.J., Comings, D.E., 2000. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J. Psychoactive Drugs 32, 1–112.
Blum, K., Gold, M., Demetrovics, Z., Archer, T., Thanos, P.K., Baron, D., Badgaiyan, R.D., 2017. Substance use disorder a bio-directional subset of reward deficiency syndrome. Front. Biosci. (Landmark Ed.) 22, 1534–1548.
Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173.
Daglish, M.R., Weinstein, A., Malizia, A.L., Wilson, S., Melichar, J.K., Britten, S., Brewer, C., Lingford-Hughes, A., Myles, J.S., Grasby, P., Nutt, D.J., 2001. Changes in regional cerebral blood flow elicited by craving memories in abstinent opiate-dependent subjects. Am. J. Psychiatry 158, 1680–1686.
Deng, X.D., Jiang, H., Ma, Y., Gao, Q., Zhang, B., Mu, B., Zhang, L.X., Zhang, W., Er, Z.E., Xie, Y., Liu, Y., 2015. Association between DRD2/ANKK1 TaqIA polymorphism and common illicit drug dependence: evidence from a meta-analysis. Hum. Immunol. 76, 42–51.
Di Simplicio, M., Norbury, R., Harmer, C.J., 2012. Short-term antidepressant administration reduces negative self-referential processing in the medial prefrontal cortex in subjects at risk for depression. Mol. Psychiatry 17, 503–510.
Eisenstein, S.A., Bogdan, R., Love-Gregory, L., Corral-Frias, N.S., Koller, J.M., Black, K.J., Moerlein, S.M., Perlmutter, J.S., Barch, D.M., Hershey, T., 2016. Prediction of striatal D2 receptor binding by DRD2/ANKK1 TaqIA allele status. Synapse 70, 418–431.
Fareed, A., Vayalapalli, S., Stout, S., Casarella, J., Drexler, K., Bailey, S.P., 2011. Effect of methadone maintenance treatment on heroin craving, a literature review. J. Addict. Dis. 30, 27–38.
Filbey, F.M., Claus, E.D., Morgan, M., Forester, G.R., Hutchison, K., 2012. Dopaminergic genes modulate response inhibition in alcohol abusing adults. Addict. Biol. 17, 1046–1056.
Franklin, T.R., Wang, Z., Wang, J., Sciortino, N., Harper, D., Li, Y., Ehrman, R., Kampman, K., O'Brien, C.P., Detre, J.A., Childress, A.R., 2007. Limbic activation to cigarette smoking cues independent of nicotine withdrawal: a perfusion fMRI study. Neuropsychopharmacology 32, 2301–2309.
Goto, Y., Grace, A.A., 2005. Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. Nat. Neurosci. 8, 805–812.
Gu, H., Salmeron, B.J., Ross, T.J., Geng, X., Zhan, W., Stein, E.A., Yang, Y., 2010. Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. Neuroimage 53, 593–601.
Haber, S.N., Knutson, B., 2010. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35, 4–26.
Hahn, B., Ross, T.J., Yang, Y., Kim, I., Huestis, M.A., Stein, E.A., 2007. Nicotine enhances visuospatial attention by deactivating areas of the resting brain default network. J. Neurosci. 27, 3477–3489.
Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32, 50–55.
Hou, Q.F., Li, S.B., 2009. Potential association of DRD2 and DAT1 genetic variation with heroin dependence. Neurosci. Lett. 464, 127–130.
Kreek, M.J., Levran, O., Reed, B., Schlussman, S.D., Zhou, Y., Butelman, E.R., 2012. Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics. J. Clin. Invest. 122, 3387–3393.
Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog. Neurobiol. 72, 341–372.
Langleben, D.D., Ruparel, K., Elman, I., Busch-Winokur, S., Pratiwadi, R., Loughead, J., O'Brien, C.P., Childress, A.R., 2008. Acute effect of methadone maintenance dose on brain FMRI response to heroin-related cues. Am. J. Psychiatry 165, 390–394.
Langleben, D.D., Ruparel, K., Elman, I., Loughead, J.W., Busch, E.L., Cornish, J., Lynch, K.G., Nuwayser, E.S., Childress, A.R., O'Brien, C.P., 2014. Extended-release naltrexone modulates brain response to drug cues in abstinent heroin-dependent patients. Addict. Biol. 19, 262–271.
Lawford, B.R., Young, R.M., Noble, E.P., Sargent, J., Rowell, J., Shadforth, S., Zhang, X., Ritchie, T., 2000. The D(2) dopamine receptor A(1) allele and opioid dependence: association with heroin use and response to methadone treatment. Am. J. Med. Genet. 96, 592–598.
Li, Q., Wang, Y., Zhang, Y., Li, W., Yang, W., Zhu, J., Wu, N., Chang, H., Zheng, Y., Qin, W., Zhao, L., Yuan, K., Liu, J., Wang, W., Tian, J., 2012. Craving correlates with mesolimbic responses to heroin-related cues in short-term abstinence from heroin: an event-related fMRI study. Brain Res. 1469, 63–72.
Li, Q., Wang, Y., Zhang, Y., Li, W., Zhu, J., Zheng, Y., Chen, J., Zhao, L., Zhou, Z., Liu, Y., Wang, W., Tian, J., 2013. Assessing cue-induced brain response as a function of abstinence duration in heroin-dependent individuals: an event-related fMRI study. PLoS One 8, e62911.
Li, Q., Li, W., Wang, H., Wang, Y., Zhang, Y., Zhu, J., Zheng, Y., Zhang, D., Wang, L., Li, Y., Yan, X., Chang, H., Fan, M., Li, Z., Tian, J., Gold, M.S., Wang, W., Liu, Y., 2015. Predicting subsequent relapse by drug-related cue-induced brain activation in heroin addiction: an event-related functional magnetic resonance imaging study. Addict. Biol. 20, 968–978.
Martinez, D., Saccone, P.A., Liu, F., Slifstein, M., Orlowska, D., Grassetti, A., Cook, S., Broft, A., Van Heertum, R., Comer, S.D., 2012. Deficits in dopamine D(2) receptors and presynaptic dopamine in heroin dependence: commonalities and differences with other types of addiction. Biol. Psychiatry 71, 192–198.
Matzeu, A., Cauvi, G., Kerr, T.M., Weiss, F., Martin-Fardon, R., 2017. The paraventricular nucleus of the thalamus is differentially recruited by stimuli conditioned to the availability of cocaine versus palatable food. Addict. Biol. 22, 70–77.
Pohjalainen, T., Rinne, J.O., Nagren, K., Lehikoinen, P., Anttila, K., Syvalahti, E.K., Hietala, J., 1998. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. Mol. Psychiatry 3, 256–260.
Ponce, G., Quinones-Lombrana, A., Martin-Palanco, N.G., Rubio-Solsona, E., Jimenez-Arriero, M.A., Palomo, T., Hoenicka, J., 2016. The addiction-related gene Ankk1 is oppositely regulated by D1R- and D2R-like dopamine receptors. Neurotox. Res. 29, 345–350.
Richter, A., Richter, S., Barman, A., Soch, J., Klein, M., Assmann, A., Libeau, C., Behnisch, G., Wustenberg, T., Seidenbecher, C.I., Schott, B.H., 2013. Motivational salience and genetic variability of dopamine D2 receptor expression interact in the modulation of interference processing. Front. Hum. Neurosci. 7, 250.
Richter, A., Barman, A., Wustenberg, T., Soch, J., Schanze, D., Deibele, A., Behnisch, G., Assmann, A., Klein, M., Zenker, M., Seidenbecher, C., Schott, B.H., 2017. Behavioral and neural manifestations of reward memory in carriers of low-expressing versus high-expressing genetic variants of the dopamine D2 receptor. Front. Psychol. 8, 654.
Ritchie, T., Noble, E.P., 2003. Association of seven polymorphisms of the D2 dopamine receptor gene with brain receptor-binding characteristics. Neurochem. Res. 28, 73–82.
Rushworth, M.F., Walton, M.E., Kennerley, S.W., Bannerman, D.M., 2004. Action sets and

decisions in the medial frontal cortex. Trends Cogn. Sci. (Regul. Ed.) 8, 410–417.
Sinha, R., 2013. The clinical neurobiology of drug craving. Curr. Opin. Neurobiol. 23, 649–654.
Stelzel, C., Basten, U., Montag, C., Reuter, M., Fiebach, C.J., 2010. Frontostriatal involvement in task switching depends on genetic differences in d2 receptor density. J. Neurosci. 30, 14205–14212.
Tiffany, S.T., Carter, B.L., 1998. Is craving the source of compulsive drug use? J. Psychopharmacol. 12, 23–30.
Uhl, G., Blum, K., Noble, E., Smith, S., 1993. Substance abuse vulnerability and D2 receptor genes. Trends Neurosci. 16, 83–88.
Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Ding, Y.S., Sedler, M., Logan, J., Franceschi, D., Gatley, J., Hitzemann, R., Gifford, A., Wong, C., Pappas, N., 2001. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am. J. Psychiatry 158, 2015–2021.
Walter, M., Denier, N., Gerber, H., Schmid, O., Lanz, C., Brenneisen, R., Riecher-Rossler, A., Wiesbeck, G.A., Scheffler, K., Seifritz, E., McGuire, P., Fusar-Poli, P., Borgwardt, S., 2015. Orbitofrontal response to drug-related stimuli after heroin administration. Addict. Biol. 20, 570–579.
Wang, W., Li, Q., Wang, Y., Tian, J., Yang, W., Li, W., Qin, W., Yuan, K., Liu, J., 2011. Brain fMRI and craving response to heroin-related cues in patients on methadone maintenance treatment. Am. J. Drug Alcohol Abuse 37, 123–130.
Wang, Y., Wang, H., Li, W., Zhu, J., Gold, M.S., Zhang, D., Wang, L., Li, Y., Yan, X., Cheng, J., Li, Q., Wang, W., 2014. Reduced responses to heroin-cue-induced craving in the dorsal striatum: effects of long-term methadone maintenance treatment. Neurosci. Lett. 581, 120–124.
Xu, K.Z., Anderson, B.A., Emeric, E.E., Sali, A.W., Stuphorn, V., Yantis, S., Courtney, S.M., 2017. Neural basis of cognitive control over movement inhibition: human fMRI and primate electrophysiology evidence. Neuron 96 1447–1458 e1446.
Zijlstra, F., Booij, J., van den Brink, W., Franken, I.H., 2008. Striatal dopamine D2 receptor binding and dopamine release during cue-elicited craving in recently abstinent opiate-dependent males. Eur. Neuropsychopharmacol. 18, 262–270.
Zijlstra, F., Veltman, D.J., Booij, J., van den Brink, W., Franken, I.H., 2009. Neurobiological substrates of cue-elicited craving and anhedonia in recently abstinent opioid-dependent males. Drug Alcohol Depend. 99, 183–192.