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Identifying new susceptibility genes on dopaminergic and serotonergic pathways for the framing effect in decision-making

G ,[1,2] J L ,[3,4] G [5] J [6] F [7,8]
H n ,[7,8] L ,[1,7,9] [1,2,9,10,11]

[1]C B C [2] C , B 100871, C , [3]C C E [4] C
B F , , G 518060, C , [5]K L
B B C (E), ,
710069, C , [6] I E , C , G
510631, C , [7] C L , [8] L [9] K -IDG/ G
I B , [10]K L (E), [11]B K
L B H , , B 100871, C

G J L .
C , C , 5 , B 100871,
C . E : 104@ . .

Abstract

- (*SLC6A4*) - (*COMT*) , 26 1317 C H .
C *SLC6A4* *COMT* -
-L- -
(*DDC*) , , -

Key words: ; *DDC*; *COMT*; *SLC6A4*; G A

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Introduction

D [illegible] (. . [illegible]) [illegible] (. . [illegible]), [illegible] ' (K [illegible] , 1981; K [illegible] , 1984; K [illegible] et al., 1999). [illegible] (K [illegible] , 1979; [illegible] , 1997), [illegible] et al., 1982; D [illegible] , 2004). [illegible] , 2008). [illegible] (D [illegible] et al., 2006; [illegible] et al., 2009; [illegible] et al., 2013; G et al., 2016). [illegible] (D [illegible] D [illegible] , 2008), [illegible] ([illegible] C , 2011). [illegible] (K [illegible] , 1979; [illegible] , 1997; D [illegible] et al., 2006; [illegible] et al., 2009; G et al., 2016), [illegible] ([illegible] , 2011; C [illegible] et al., 2012; C [illegible] , 2012), [illegible] . A [illegible] (C [illegible] et al., 2009; D [illegible] et al., 2009; K [illegible] C , 2009; H et al., 2010; F [illegible] et al., 2011; H [illegible] et al., 2012; [illegible] et al., 2013; [illegible] et al., 2014), [illegible] (C [illegible] et al., 2009, = 36; et al., 2009, = 30) 5-H L [illegible] , [illegible] (SLC6A4), [illegible] ( ) 5-H L [illegible] ( ) . [illegible] (= 98) [illegible] COMT COMT _ 158 [illegible] C [illegible] _ / _ [illegible] , [illegible] , [illegible] (G et al., 2016). H , [illegible] (, 2009; [illegible] et al., 2010), [illegible] H [illegible] . G [illegible] (-L [illegible] 2010; [illegible] et al., 2010; [illegible] et al., 2010; G et al., 2014). F [illegible] , COMT [illegible] (. [illegible]) [illegible] ([illegible] et al., 1998; E et al., 2003; [illegible] et al., 2003; G et al., 2004; [illegible] et al., 2005; D et al., 2006; K -K [illegible] et al., 2007; [illegible] et al., 2007; [illegible] et al., 2008; [illegible] et al., 2010; [illegible] , H [illegible] , 2006). [illegible] , [illegible] - MAOA MAOB) [illegible] (D [illegible] et al., 2009) - [illegible] (K [illegible] et al., 2007; et al., 2009) . G [illegible] (-L [illegible] 2010; [illegible] et al., 2010; B [illegible] G [illegible] , 2011; F [illegible] et al., 2013; J L , 2014). , [illegible] (/), ( ) 5-H L [illegible] (H et al., 2002; C et al., 2005; H et al., 2005) [illegible] - (et al., 2014); [illegible] (B et al., 1998; L , 2004; L - [illegible] et al., 2005; G [illegible] , 2010), [illegible] - [illegible] 5-H L [illegible] 5-H L LE [illegible] ([illegible] et al., 2009). , [illegible] , [illegible] -L- [illegible] - [illegible] (DDC), , [illegible] (C et al., 2010) (B [illegible] et al., 2003). C [illegible] , [illegible] I [illegible] , [illegible] - [illegible] (C [illegible]) ([illegible] A , 2008; H et al., 2011 ,) - ([illegible] et al., 2007; [illegible] et al., 2010) [illegible] - (G A) , [illegible] , 26 [illegible] - [illegible] . A [illegible] KEGG (:// [illegible] / [illegible]), [illegible] - ([illegible] et al., 2011; et al., 2014; B [illegible] et al., 2016). G [illegible] . G [illegible] ( ) [illegible] G A , - [illegible] (LD) [illegible] ([illegible] A , 2008) [illegible] ([illegible] et al., 2010). [illegible] , [illegible] - C [illegible] - [illegible] (C) [illegible] ([illegible] , 2004; [illegible] A , 2008).

[illegible] (. . [illegible]) [illegible] (. . [illegible], 2004; K et al., 2008; [illegible] A , 2008). C [illegible] et al., 2010; et al., 2014) [illegible] ([illegible] A , 2008; H et al., 2011 ,).

Materials and methods

Participants

[illegible] (G 2013) C [illegible], C , [illegible] C H [illegible] (80.1% [illegible], [illegible] 18.66 ± 0.90) [illegible] . 15 . A [illegible] 100 [illegible] behavioral test; D et al., 2006; G et al., 2016). I 1582 , 5 , [illegible] A [illegible] 1317 [illegible] . [illegible] , [illegible] ([illegible]). A [illegible] (. . <50, [illegible] = 30.58, D = 5.35) [illegible] A ([illegible] 1971; [illegible] et al., 1999) [illegible] (. . <50, [illegible] = 33.3, D = 6.31) [illegible] D ([illegible] 1965; [illegible] et al., 1999), [illegible] (51, 51, 53, 53, 53, 54, 54, 55 59,) [illegible] (51, 51 56,) [illegible] . G [illegible] 12 [illegible] , [illegible] . [illegible] . [illegible] D H E C [illegible] C [illegible] , [illegible] .

The behavioral test

[illegible] G et al. (2016), D et al (2006) [illegible] et al., 2009; [illegible] et al., 2013). A [illegible] , [illegible] . [illegible] (. . [illegible]) [illegible] , [illegible] (. . [illegible]). [illegible] (. . [illegible]) (. [illegible] K 20 [illegible] 50') [illegible] (. . [illegible]) (. [illegible] L 30 [illegible] 50'), . [illegible] . F [illegible] , [illegible] . F , [illegible] (. [illegible] K 80 [illegible] 100' vs K 100 40%'). [illegible] . [illegible] . E 48 (16 [illegible] , 16 [illegible] 16), [illegible] . [illegible] D et al. (2006). [illegible] . A [illegible] (500:1) [illegible] . G et al. (2016) [illegible] . [illegible] (<75%, [illegible] =57.9%±17.6%; 1317 , [illegible] = 90.5%±6.5%) [illegible] . [illegible] (4.44%±1.75%) [illegible] 1317 (14.51%±0.34%), $t_{(1580)} = 9.16$, $P < 0.001$. F [illegible] , [illegible] ([illegible]).

[illegible] ([illegible] = 1591[illegible] , D = 551[illegible]) [illegible] ([illegible] = 1601[illegible] , D = 544[illegible]) [illegible] ([illegible] = 1776[illegible] , D = 353[illegible] ; [illegible] = 1872[illegible] , D = 376[illegible]), $t_{(1580)} = 6.639$, $P < 0.001$ $t_{(1580)} = 9.375$, $P < 0.001$ [illegible] , [illegible] .

Genotyping

[illegible] - [illegible] D A [illegible] G -610L [illegible] A I [illegible] . [illegible] I [illegible] H [illegible] -8 1 C [illegible] I [illegible] .

Gene selection and preprocessing

[illegible] - [illegible] K E G G [illegible] (KEGG; ://[illegible] / [illegible]). [illegible] ( ) [illegible] (TH), [illegible] -L- [illegible] - [illegible] (DDC), [illegible] (VMAT2) , ( ) [illegible] (DRD1–5), ( ) [illegible] (DAT1, [illegible]

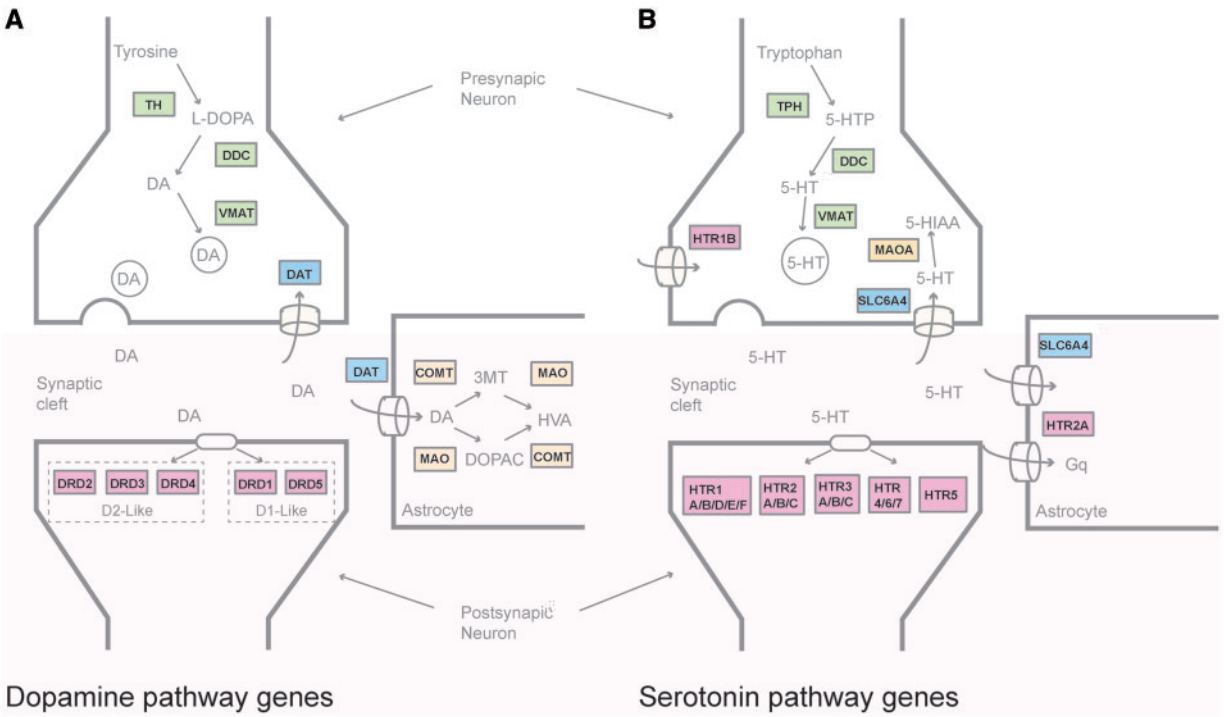

Fig. 1. D (A) (B) - ( ), ( ), ( ). C - K E G G (KEGG; :// /); , *et al.*, 2014.

SLC6A3), -O- (COMT), - A (MAOA) B (MAOB) (, *et al.*, 2011; *et al.*, 2014) ( ) 5- - (TPH 1 TPH2) , ( ) 5- (HTR1A/B/D/E/F, HTR2A/B/C, HTR3A/B/C/D/E, HTR4, HTR5A/B, HTR6-7, HTRA1-4) , ( ) - - (SLC6A4) (B *et al.*, 2016) (F 1). HTR3D HTR3E (*et al.*, 2003; B : G E E , :// . /). DRD4, DRD5, HTR1A/B/D/F, HTR5B, HTRA2 HTRA4 . G A LI K (*et al.*, 2007; *et al.*, 2014): ( ) , H E 10^{-4} (AF) 0.1 0.05; ( ) 0.05 ( ) . - , G A (D) - LI K (*et al.*, 2006; *et al.*, 2007) . LI K (*et al.*, 2007) (*et al.*, 2006). F , 19 .

Principle component analysis

A (C :// . - .). LD G A (CA) - LD (A , 2008). , (C) 90% (A , 2008; *et al.*, 2014). (LD), C - . C LD (D *et al.*, 2001; *et al.*, 2001; G *et al.*, 2002), (1). F , 6 90.2% DDC 47 G A .

Gene-behavior association analysis

-F (. .) (A , 2008; H *et al.*, 2011 ,). -F . F

Table 1. [illegible]

	F[illegible]	G	C	%	R^2	A	R^2	Partial-F	p_{unc}	p_{perm}	p_{emp}
D		*TH*	2	2	100	0.001	<0.001	0.712	0.491	0.484	0.485
		DDC	47	6	90	0.010	0.006	2.329	0.031*	0.031*	0.038*
		VMAT2	17	9	90	0.003	<0.001	0.501	0.875	0.878	0.862
	/	*DAT1*	16	6	91	0.005	<0.001	1.027	0.406	0.408	0.466
	C	*COMT*	18	6	91	0.012	0.009	2.648	0.015*	0.014*	0.027*
		MAOA	6	3	90	0.003	<0.001	1.143	0.331	0.325	0.346
		MAOB	37	5	92	0.005	0.002	1.367	0.234	0.232	0.293
		DRD1	1	1	100	0.000	<0.001	0.097	0.756	0.756	0.780
		DRD2	16	8	90	0.004	<0.001	0.721	0.673	0.680	0.770
		DRD3	41	12	92	0.014	0.006	1.617	0.081	0.081	0.099
		TPH1	2	2	100	0.001	<0.001	0.719	0.487	0.476	0.477
		TPH2	6	4	93	0.002	<0.001	0.519	0.721	0.718	0.753
		SLC6A4	8	3	90	0.006	0.004	2.795	0.039*	0.038*	0.037*
		HTR1E	16	6	91	0.007	0.003	1.545	0.160	0.158	0.199
		HTR2A	44	12	90	0.013	0.005	1.492	0.120	0.121	0.123
		HTR2B	3	2	100	0.001	<0.001	0.596	0.551	0.551	0.519
		HTR2C	22	8	90	0.006	<0.001	0.920	0.499	0.499	0.517
		HTR3A	4	4	100	0.001	<0.001	0.364	0.834	0.831	0.833
		HTR3B	22	6	90	0.001	<0.001	0.228	0.968	0.967	0.970
		HTR3C	2	1	99	0.000	<0.001	0.124	0.725	0.724	0.677
		HTR4	46	14	91	0.015	0.005	1.422	0.135	0.136	0.075
		HTR5A	7	4	92	0.006	0.003	1.866	0.114	0.114	0.118
		HTR6	2	1	100	0.000	<0.001	0.000	0.990	0.992	0.982
		HTR7	22	6	93	0.006	0.002	1.316	0.247	0.242	0.301
		HTRA1	34	9	91	0.007	<0.001	0.974	0.460	0.456	0.441
		HTRA3	19	5	92	0.004	0.001	1.133	0.341	0.356	0.370

C , [illegible] ; % , [illegible] C ; p_{unc}, P [illegible] F- ; p_{perm}, [illegible] P ; p_{emp}, [illegible] P .
* P < 0.05.

[illegible] , [illegible] -F [illegible] , [illegible] , [illegible] - [illegible] ([illegible]) [illegible] , [illegible] , [illegible] , [illegible] [illegible] (*Principle component analysis*) [illegible] . E [illegible] F , [illegible] , [illegible] . [illegible] -F [illegible] (1) (H *et al.*, 2011). *k* ( )– ( ) [illegible] :

$$Fk, df(full) = \frac{RSS(reduced) - RSS(full)}{df(reduced) - df(full)} / \frac{RSS(full)}{df(full)} \quad (1)$$

, A A/B [illegible] - [illegible] - [illegible] , [illegible] [illegible] - [illegible] . C [illegible] - [illegible] [illegible] (, 2003), [illegible] = 0.62% ± 0.08% (E) (1). A , [illegible] - [illegible] - [illegible] , [illegible] [illegible] (*COMT*, *SLC6A*, *DDC* *MAOB*; *Gene-behavior association results*). [illegible] - [illegible] , [illegible] , [illegible] [illegible] - [illegible] . C [illegible] - [illegible] [illegible] [illegible] (*COMT*: P = 0.028, *SLC6A4*: P = 0.038, *DDC*: P = 0.070 , *MAOB*: P = 0.029 [illegible]), [illegible] - [illegible] .

Permutation tests

[illegible] , [illegible] C [illegible] [illegible] (H *et al.*, 2011 ; *et al.*, 2014). [illegible] - [illegible] (B [illegible] , 2001; [illegible] , 2004; C [illegible] *et al.*, 2008; G [illegible] - [illegible] *et al.*, 2014), [illegible] [illegible] [illegible] - [illegible] [illegible] [illegible] (. . [illegible] - P). [illegible] [illegible] (C [illegible] , 2001).

Empirical tests

[illegible] [illegible] [illegible]

[illegible]

Protein–protein interactions

[illegible]

SNP–SNP interactions

[illegible]

Results

Behavioral results

[illegible]

: 59.75%±0.47% (E) [illegible] *vs* 45.23% ± 0.46% [illegible], $t_{(1316)} = 42.08$, $P < 0.0001$. [illegible] 2010), 2 ([illegible] : F [illegible] *vs*) × 2 ([illegible] : [illegible] *vs*) [illegible] (A _ A) [illegible], $F_{(1, 1315)} = 15.587$, $P < 0.001$, $F_{(1, 1314)} = 14.701$, $P < 0.001$, [illegible] $\beta = -0.052$, $t = -1.903$, $P = 0.057$. [illegible] *et al.*, 2011). [illegible]

Gene-behavior association results

[illegible] *et al.*, 2016), [illegible] R^2 [illegible] $= 0.009$, -F = 2.648, $P = 0.015$. [illegible] *et al.* (2009) [illegible] 5-H L [illegible] *SLC6A4* [illegible] 0.4% [illegible] R^2 [illegible] $= 0.004$, -F = 2.795, $P = 0.039$. I [illegible] *DDC* [illegible] R^2 [illegible] $= 0.006$, -F = 2.329, $P = 0.031$, [illegible] 0.6% [illegible] 1). [illegible] 10 000 [illegible] ([illegible] 1), *COMT*: [illegible] $P = 0.014$, *SLC6A4*: [illegible] $P = 0.038$, *DDC*: [illegible] $P = 0.031$. G [illegible] (FD) [illegible] D [illegible]). [illegible] G A [illegible] . D [illegible] 1), [illegible] ([illegible] 1), *COMT*: [illegible] $P = 0.027$, *SLC6A4*: [illegible] $P = 0.037$, *DDC*: [illegible] $P = 0.038$. B [illegible] *MAOA/B* [illegible]

. [illegible] MAOB [illegible] - [illegible] 2.8% [illegible] R^2 [illegible] $=0.028$, -$F=2.499$, $P=0.031$. [illegible] ($P=0.038$) [illegible] ($P=0.043$). [illegible] MAOA [illegible] . [illegible] CA [illegible] - , - , - [illegible] . H , [illegible] . DDC [illegible] SLC6A4 [illegible] , COMT [illegible] MAOB [illegible] . - [illegible] ([illegible] 3). [illegible] I G [illegible] (COMT, SLC6A4, DDC MAOB) - [illegible] ([illegible] F [illegible] 1). G CA [illegible] - [illegible] (H , 1975), [illegible] - [illegible] . - [illegible] F [illegible] 2 ([illegible]). F COMT [illegible] , [illegible] 4680 [illegible] , LD CHB): 15.1863 0 D 5

[illegible]

[illegible] *DDC* [illegible] *MAOB* [illegible]

[illegible]

FC- [illegible] .

B , K.L., , D. . (2010). I . *Neuroimage*, **53**(3), 804 9.

B , A., K , G., C , ., *et al.* (2003). - - D A - . *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, **117**(1), 18 22.

B , ., H , J. (2006). E – . *BMC Bioinformatics*, **7**(1), 1.

B , C., H , C., G , A. (2004). C . *BMC Bioinformatics*, **5**(1), 1.

C , A., A , F., H., H. (2008). . *Source Code for Biology and Medicine*, **3**, 15.

C , ., , K., H , B. ., F , A., C , . ., L , K. . (2005). B : . *Proceedings of the National Academy of Sciences of the United States of America*, **102**(34), 12224 9.

C , D., J , ., , .K., , B. (2012). . *Management Science*, **58**(1), 21 34.

C , J. . (2001). A . *Heredity (Edinb)*, **87**(1), 52 8.

C , ., , A.C., , . . (2008). . *Trends in Cognitive Sciences*, **12**(1), 31 40.

C , J., G , ., E , G., *et al.* (2010). A 44 . *Journal of Psychiatric Research*, **44**(11), 717 24.

C , H., , . (2012). . *Claremont McKenna College Robert Day School of Economics and Finance Research Paper* (2012-01).

C , L.G., , ., , ., *et al.* (2009). G . *Social Cognitive and Affective Neuroscience*, **4**(4), 399 408.

[illegible] . *Cognitive, Affective, & Behavioral Neuroscience*, **12**(4), 678 91.

H , D. ., K , ., , J.L., C .-C., , . . (2011). [illegible] . *Frontiers in Genetics*, **2**, 73.

H , D. ., , J.L., K , ., *et al.* (2011). [illegible] - (G A): [illegible] - 731 [illegible] . *Neuroimage*, **56**(4), 1875 91.

H , E., B , ., F , . (2004). B : [illegible] - [illegible] . *J Autism and Developmental Disorders*, **34**(2), 229 35.

H [illegible] ., [illegible] L. (2010). [illegible] . *Personality and Individual Differences*, **48**(5), 649 53.

I [illegible] , K., K [illegible] , K., [illegible] , A., *et al.* (1999). [illegible] - [illegible] [illegible] . *Neuroscience Letters*, **269**(1), 37 40.

J , ., L , . (2014). - [illegible] (5-H L). [illegible] . *Neurobiology. Progress in Neurobiology*, **117**, 41 53.

K [illegible] , D., , A. (1979). : [illegible] . *Econometrica: Journal of the Econometric Society*, 263 91.

K [illegible] , D., , A. (1984). C , [illegible] , [illegible] . *American Psychologist*, **39**(4), 341.

K [illegible] .J., , .K., L , .J., *et al.* (2006). F [illegible] - [illegible] A A A B [illegible] [illegible] . *Movement Disorders*, **21**(12), 2175 80.

K , . ., C - , ., C , L.G., *et al.* (2002). G - [illegible] [illegible] [illegible] B 13 [illegible] . *Neurotoxicology* **23**(4), 515 9.

K [illegible] A., K , K., H [illegible] , J., *et al.* (2007). A A -A [illegible] [illegible] . *Neuropsychobiology*, **56**(56), 191 6.

K -K [illegible] B. ., G , J., [illegible] . . (2007). - [illegible] C , [illegible] H 1B, , [illegible] . *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*

, C.A., B , G.B., A , .J., *et al.* (2007). C
(158) 5H L
: m
A H C . *Genes, Brain and Behavior*, **6**(7), 647 52.
m , E. ., K , ., A m , A. (2010). D
m m m
Progress in Neurobiology, **92**(2), 112 33.
, A.L., , J., , . ., , .E., ,
.A., , D. (2006). m
m - . *Nature Genetics*, **38**(8), 904 9.
, ., , B., -B , K., *et al.* (2007). LI K:
-m m - -
. *The American Journal of Human Genetics*, **81**(3), 559 75.
, D.E., C , ., B , ., *et al.* (2001). L -
mm mm m . *Nature*, **411**(6834), 199 204.
, ., F , A., , ., , A., , ., m
C. (2013). m m m -
m m m mm m . *Frontiers in Human Neuroscience*, **7**, 242.
, A. ., G , . (2003). m m
. *Proceedings of the National Academy of Sciences*, **100**(3), 1128 33.
, J. ., , B., , G.C., *et al.* (2009). A m
m m m m m
. *Journal of Neuroscience*, **29**(18), 5985 91.
, J., D , C.J., H , E., G , K.D. (2009).
A m m -A m -
m m ADHD m mm
. *Journal of Autism & Developmental Disorders*, **39**(1), 67 74.
m - , ., D m, ., B , ., m , A. (2005).
D m m m m -
. *Clinical Neuropharmacology*, **28**(5), 228 37.
, E.E. (2009). m
mm mm . *Nature*, **461**(7261), 218 23.
, D.J. (2004). E m m
. *Genetic Epidemiology*, **27**(4), 348 64.
m , C., , ., , H.H., , L. (2010). Im m m
m m . *Neuroimage*, **53**(3), 810 21.
m , H. ., Jm m , ., , A.I., H mm, A. . (2003).
Em m m -
. *Psychological Science*, **14**(1), 7 13.
, E., , I., m, L., *et al.* (2014). D m
m m m m -
m mm . *Proceedings of the National Academy of Sciences*, **111**(26), 9615 20.
, D.J., , .B.).