

1 **Inheritance of neural substrates for motivation and pleasure experience**

2

3 Zhi Li<sup>1,2</sup>, Yi Wang<sup>1</sup>, Chao Yan<sup>3</sup>, Ke Li<sup>4</sup>, Ya-wei Zeng<sup>4</sup>, Eric F. C. Cheung<sup>5</sup>, Anna R.

4 Docherty<sup>6,7</sup>, Pak C. Sham<sup>8,9,10</sup>, Raquel E. Gur<sup>11</sup>, Ruben C. Gur<sup>11</sup>, Raymond C. K.

5 Chan<sup>1,2\*</sup>

6

7 1: Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key

8 Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences,

9 Beijing, China

10 2: Department of Psychology, the University of Chinese Academy of Sciences, Beijing,

11 China

12 3: Key Laboratory of Brain Functional Genomics (MOE and STCSM), School of

13 Psychology and Cognitive Science, East China Normal University, Shanghai, China;

14 4: MRI Center, Hospital 306, Beijing, China;

15 5: Castle Peak Hospital, Hong Kong, China;

16 6: Department of Psychiatry, University of Utah School of Medicine, Salt Lake City,

17 Utah, USA

18 7: Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth

19 University, Richmond, Virginia, USA

20 8: Centre for Genomic Sciences, the University of Hong Kong, Hong Kong, China;

21 9: State Key Laboratory in Brain and Cognitive Sciences, the University of Hong Kong,

22 Hong Kong, China;

23 10: Department of Psychiatry, the University of Hong Kong, Hong Kong, China

24 11: Department of Psychiatry, University of Pennsylvania Perelman School of

25 Medicine, Philadelphia, Pennsylvania, USA

26

27 \*correspondence should be addressed to:

28 Raymond Chan, Room 526, South Block, Institute of Psychology, Chinese Academy of

29 Sciences, 16 Lincui Road, Beijing 100101, China; Tel/Fax number: +86(0)10-64836274;

30 Email: rckchan@psych.ac.cn

31 **Abstract**

32 Despite advances in the understanding of the reward system and the role of  
33 dopamine in recent decades, the heredity of the underlying neural mechanisms is  
34 not known. In the present study, a Monetary Incentive Delay (MID) task was used to  
35 examine the haemodynamic activation of the nucleus accumbens (*NAcc*), a key hub  
36 of the reward system, in 86 healthy monozygotic twins and 88 dizygotic twins during  
37 the anticipation of monetary incentives. The participants also completed self-report  
38 measures of pleasure experience. Using a voxel-wise heritability mapping method,  
39 activation of the bilateral *NAcc* during the anticipation of monetary gains was found  
40 to have significant heritability ( $h^2 = 0.20-0.49$ ). Moreover, significant shared genetic  
41 covariance was observed between pleasure experience and *NAcc* activation when  
42 anticipating monetary gain. These findings suggest that *NAcc* activation and self-  
43 reported pleasure experience may both be heritable, and their phenotypic  
44 correlation may be partially explained by shared genetic variation.

45

46 **Keywords:** Reward System, Nucleus Accumbens, Heritability, Motivation, Pleasure

## 47 Introduction

48 The reward system plays a key role in human behaviour and emotion (*Iversen, 2010*).  
49 The nucleus accumbens (*NAcc*), situated in the ventral striatum, is regarded as the  
50 hub of the mesolimbic and mesocortical reward systems (*Baldo & Kelley, 2007*;  
51 *Berridge & Robinson, 1998; Haber & Knutson, 2010*). However, the contribution of  
52 the *NAcc* to reward processing is not fully understood. Compelling evidence supports  
53 the notion that the reward processing system can be parsed into anticipatory and  
54 consummatory phases (*Baldo & Kelley, 2007; Craig, 1917*). Dopaminergic activity in  
55 the *NAcc* is associated with salience attribution of motivation, which assigns  
56 motivational significance to different incentives in the anticipatory period (*Berridge,*  
57 *2003, 2007, 2012*). Despite these advances in understanding the reward system, the  
58 heritability of reward processing and its component phenotypes are largely unknown.

59 Studies in the last decade have suggested a relationship between dopaminergic  
60 gene variation and ventral striatal activation measured by functional MRI reward  
61 tasks in anticipating, predicting, or receiving monetary incentives (*Aarts et al., 2010*;  
62 *Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Forbes et al., 2009; Hahn et*  
63 *al., 2011; Nikolova, Ferrell, Manuck, & Hariri, 2011; Yacubian et al., 2007*). Although  
64 single genetic polymorphisms have been associated with ventral striatal activation to  
65 a modest extent, studies that examine single or few polymorphisms, are seldom  
66 replicated and tend to be underpowered. Evidence from the Psychiatric Genomics  
67 Consortium indicates that psychiatric phenotypes are polygenic, with any one gene  
68 only contributing a small amount to the overall variance. Thus, to have meaningful  
69 explanatory power, it is essential to either use genome-wide common variant data,

70 aggregating the effects of all polymorphisms, or to examine family-based genetic  
71 variation. The prediction of ventral striatal activation using polygenic risk scores for  
72 psychosis has already revealed the cumulative effect of genes (*Bossong & Kahn,*  
73 *2016; Lancaster et al., 2016*), and it is expected that related component phenotypes  
74 are similarly polygenic. However, the extent to which genetic factors influence *NAcc*  
75 and ventral striatal brain activation, particularly in the anticipatory period for reward,  
76 is not clearly understood.

77 In this study, we examined measures of shared genetic variance among  
78 dimensional psychiatric phenotypes, using a voxel-wise topographical approach to  
79 map striatal activation. While previous studies have mainly employed regions of  
80 interest methodology, voxel-wise analysis affords much finer heritability mapping,  
81 thereby reducing statistical noise in heritability estimation. Hypoactivation of the  
82 *NAcc* and the ventral striatum in anticipating monetary rewards had been reported  
83 both in patients with schizophrenia (*Radua et al., 2015*) and in their unaffected  
84 biological relatives. Probands and biological relatives also exhibit increased  
85 anhedonia that co-segregates in families (*Docherty, Sponheim, & Kerns, 2015;*  
86 *Kendler, Thacker, & Walsh, 1996; Li et al., 2015*). These results suggest that impaired  
87 motivation is associated with genetic factors underlying schizophrenia (*de Leeuw,*  
88 *Kahn, & Vink, 2015; Grimm et al., 2014; Vink et al., 2016*). Thus, mapping the  
89 heritability of brain activation in anticipating and approaching reward may help  
90 clarify its potential role as an endophenotype for psychosis (*Braff, Freedman, Schork,*  
91 *& Gottesman, 2007; Gottesman & Gould, 2003*).

92 Another important matter to consider is the similar ventral striatal dysfunction

93 reported in patients with major depressive disorder, addiction, and their family  
94 members (*Beck et al., 2009; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008; Pizzagalli*  
95 *et al., 2009; Wrase et al., 2007*). Since anhedonia and motivational deficits are also  
96 relevant to major depressive disorder, the problem of non-specificity needs to be  
97 addressed. This study aims to examine the circuitry and behavioral manifestations of  
98 dimensional clinical traits, in line with Research Domain Criteria (RDoC) (*Cuthbert,*  
99 *2014; Cuthbert & Insel, 2010*).

100 Anhedonia, the diminished ability to experience pleasure, has long been regarded  
101 as a core symptom of schizophrenia and major depression disorder (*Meehl, 1975;*  
102 *Meehl, 1990; Pizzagalli, 2014*). Cumulative evidence has also demonstrated a  
103 significant heritability estimate for anhedonia ranging from 0.3 to 0.7 (*Kendler &*  
104 *Hewitt, 1992; Linney et al., 2003; MacDonald, Pogue-Geile, Debski, & Manuck, 2001*).  
105 Although previous findings support an association between motivation-related *NAcc*  
106 activation and anhedonia traits (*Vignapiano et al., 2016; Wacker, Dillon, & Pizzagalli,*  
107 *2009*), their shared genetic covariance has not been examined. Investigating the  
108 heritability of *NAcc* activation and anhedonia could facilitate the identification of  
109 shared regions of the genome and the exploration of intervention for amotivation  
110 and anhedonia, both of which indicate poor prognosis and are refractory to currently  
111 available treatment (*Kring & Barch, 2014*).

112 In the present study, we adopted a healthy-twin design to examine the heritability  
113 of pleasure experience and its shared genetic covariance with *NAcc* activation during  
114 the anticipation of monetary rewards using the Monetary Incentive Delay Task (MID).  
115 We hypothesized that both motivation-related *NAcc* activation and pleasure

116 experience would exhibit significant heritability. We further hypothesized that  
117 motivation-related *NAcc* activation and pleasure experience would share significant  
118 genetic covariance.

119

## 120 **Results**

### 121 **Demographics**

122 The sample included 43 pairs of same-sex monozygotic (MZ) twins and 44 pairs of  
123 same-sex dizygotic (DZ) twins, who were matched in gender ratio, age, and years of  
124 education. In addition, their head motion parameters were also comparable (Table  
125 1). The MZ and DZ twins demonstrated comparable scores on the Temporal  
126 Experience Pleasure Scale (TEPS), whereas DZ twins scored lower than MZ twins on  
127 the revised Chinese versions of Chapman Social Anhedonia Scale (RCSAS) and  
128 Chapman Physical Anhedonia Scale (RCPAS). The ICC of RCPAS and TEPS scores  
129 among the MZ twins were twice that of the DZ twins. However, the ICC of RCSAS  
130 scores among MZ and DZ twins did not significantly vary from 0 (Table 1). These  
131 findings suggest that in this healthy sample, there was insufficient power to detect  
132 significant genetic or phenotypic variation in RCSAS scores.

133

### 134 **Brain activation in contrast [Gain vs. No-incentive] of MID task**

135 For this contrast, during the anticipatory phase, there was significant activation of  
136 the bilateral *NAcc* and the thalamus in all participants. Activation of the bilateral

137 *NAcc* was also observed in MZ and DZ twins respectively. Furthermore, activation of  
138 the left insula was observed in MZ twins, whereas activation of the right insula was  
139 observed in DZ twins (Table 2 & Figure 1B).

140

#### 141 **Brain activation in contrast [Loss vs. No-incentive] of MID task**

142 Significant activation of the bilateral *NAcc* and the thalamus were observed in the  
143 contrast [Loss vs. No-incentive] during the anticipatory phase in all participants.

144 Significant activation of the bilateral *NAcc* was observed in both MZ and DZ twins,  
145 while activation of the left globus pallidus and the right thalamus was observed in  
146 MZ twins and DZ twins respectively (Table 2 & Figure 1B).

147

#### 148 **Heritability brain mapping**

149 In the voxel-by-voxel heritability brain mapping, two clusters were detected with  
150 significant heritability in the contrast [Gain vs. No-incentive]. The right one contained  
151 33 voxels, while the left one contained 15 voxels. The coordinates of the peak point  
152 of the two clusters were [9,15,-3] and [-9,18,-6], which were located at the right  
153 *NAcc* and the left *NAcc* respectively (Figure 3). The  $h^2$  of each voxel within both  
154 clusters ranged from 0.2 to 0.49, and the average  $h^2$  was 0.34 (Figure 3). However,  
155 we did not find any significant heritability for the contrast [Loss vs. No-incentive].

156

#### 157 **Genetic model fitting**



158 As shown in Table 3, the Cholesky trivariate model (AIC = 382.4) was not worse than  
159 the saturated model (AIC = 406.45) ( $\Delta - 2LL = 41.94$ ,  $\Delta df = 33$ ,  $p = 0.14$ ). The nested  
160 sub-models were compared with the trivariate model. A marginally significant  
161 deterioration emerged when all the additive genetic paths (a11, a12, a13, a22, a23,  
162 a33) were deleted ( $\Delta - 2LL = 12.59$ ,  $\Delta df = 6$ ,  $p = 0.05$ ), whereas the model did not  
163 worsen when we discarded all the common environmental paths (c11, c12, c13, c22,  
164 c23, c33) ( $\Delta - 2LL = 0.25$ ,  $\Delta df = 6$ ,  $p = 1$ ). Results of model comparison indicated that  
165 additive genetic factors, rather than common environmental factors, significantly  
166 contributed to the full model. The trivariate AE model (AIC = 370.65) was adopted  
167 for the subsequent parameter dropping and model comparison. After dropping one  
168 path, Model X (with path e21 dropped) was found to have the smallest AIC (368.66)  
169 in its class and was hence adopted ( $\Delta - 2LL = 0.01$ ,  $\Delta df = 1$ ,  $p = 0.94$ ). Based on Model  
170 X, a second path was further discarded. Finally, Model XV (with paths e21 and e31  
171 dropped) had the smallest AIC (367.35) among all the tested models and was  
172 selected as the best model ( $\Delta - 2LL = 0.69$ ,  $\Delta df = 1$ ,  $p = 0.4$ ). A third path was further  
173 dropped based on Model XV, but all the sub-models significantly deteriorated  
174 compared with Model XV.

175 In the best-fitting Model XV (Figure 4), the  $h^2$  of bilateral *NAcc* activation during  
176 the anticipation of monetary gain was 0.43 [95% Confidential Interval (CI): 0.19-0.62],  
177 the  $h^2$  of RCPAS scores was 0.61 (95%CI: 0.39-0.75), and the  $h^2$  of TEPS scores was  
178 0.29 (95%CI: 0.01-0.54). *NAcc* activation shared the same genes with RCPAS ( $r_g = -$   
179 0.45) and TEPS ( $r_g = 0.59$ ) scores. In addition, scores on the RCPAS and the TEPS were  
180 also influenced by some of the same genes ( $r_g = -0.72$ ). Addictive genetic factors

181 contributed almost 100% to the phenotypic correlation between *N*Acc activation and  
182 RCPAS scores ( $r_{ph} = -0.23$ ,  $r_{ph(g)} = -0.23$ ) and between *N*Acc activation and TEPS scores  
183 ( $r_{ph} = 0.21$ ,  $r_{ph(g)} = 0.21$ ). Sixty-four percent of the phenotypic correlation between  
184 RCPAS and TEPS scores ( $r_{ph} = -0.47$ ) was attributed to additive genetic factors ( $r_{ph(g)} =$   
185  $-0.3$ ), while 36% of the correlation was attributed to environmental factors ( $r_{ph(e)} =$   
186  $0.17$ ).

187

## 188 Discussion

189 This is the first biometrical study to examine the heritability of neural substrates  
190 underlying reward processing and the shared genetic covariance of motivation-  
191 related *N*Acc activation and pleasure experience. Consistent with our hypothesis,  
192 activation in the bilateral *N*Acc during the anticipation of monetary gain was  
193 significantly heritable. The heritability estimate of each voxel within the bilateral  
194 *N*Acc, while low-to moderate, was significant and ranged from 0.2 to 0.49, whilst the  
195 heritability estimate of *N*Acc activation as a whole was 0.43. RCPAS and the TEPS also  
196 exhibited significant heritability in healthy twins, at 0.61 and 0.29 respectively. Even  
197 with a modest sample size for ACE modeling, motivation-related *N*Acc activation  
198 evidenced significant shared genetic covariation with both self-reported measures of  
199 pleasure experience. This suggests that the significant phenotypic correlation  
200 between *N*Acc activation and pleasure experience is partially accounted for by  
201 shared genetic variation.

202 Bilateral *N*Acc activation during the anticipatory phase for monetary incentives,

203 found in our whole brain analysis, is consistent with previous findings (*Knutson, Fong,*  
204 *Adams, Varner, & Hommer, 2001; Knutson & Greer, 2008; Knutson, Westdorp, Kaiser,*  
205 *& Hommer, 2000*), which supports the validity of the MID task in correlating with  
206 *NAcc* activation *in vivo*. Evidence from animal studies supports the role of dopamine  
207 within the *NAcc* in salience attribution, an essential component of motivation and  
208 goal-directed behaviour formulation (*Berridge, 2007, 2012; Berridge & Robinson,*  
209 *1998*). Although fMRI measures brain haemodynamics rather than neurotransmitter  
210 chemistry, previous studies have linked activation at the *NAcc* and the ventral  
211 striatum in rewarding tasks to local dopaminergic activity. Amphetamine-induced  
212 dopamine release at the *NAcc* has been associated with local haemodynamic  
213 activation in reward processing (*Knutson & Gibbs, 2007; Oswald et al., 2007*). These  
214 data suggest that *NAcc* activation measured through fMRI could indirectly reflect  
215 local dopaminergic activity. In addition, polymorphisms of dopamine have been  
216 associated with ventral striatal activation in reward processing, suggesting that  
217 facets of the mesolimbic reward system may be heritable (*Dreher et al., 2009; Forbes*  
218 *et al., 2009; Yacubian et al., 2007*). Indeed, significant MZ twin correlation in *NAcc*  
219 activation has previously been reported (*Silverman et al., 2014*). In the present study,  
220 we corroborated previous findings through quantifying the genetic and  
221 environmental effects on the motivation-related *NAcc* activation. Stokes and  
222 colleagues (2013) reported a significant heritability estimate of 0.21 for  
223 dopaminergic activities of the right ventral striatum in the resting state. In this study,  
224 we found a heritability estimate of 0.4 for bilateral *NAcc* activation in anticipating  
225 monetary gains. The considerably larger sample size in this study, relative to

226 previous research, lends further support to this finding.

227 Quantifying the heritability of *NAcc* activation in anticipating monetary incentives  
228 could facilitate our understanding of the genetic effect on reward processing and  
229 detection of associated genetic loci. Voxel-wise heritability estimation is an  
230 alternative methodology that may be more sensitive in detecting genetic effects, and  
231 as such may supplement findings from previous regions of interest analysis often  
232 limited by small sample sizes. Across single-gene polymorphism studies (*Dreher et al.,*  
233 *2009; Forbes et al., 2009; Yacubian et al., 2007*), twin studies (*Silverman et al., 2014*)  
234 or studies estimating the heritability of striatal dopaminergic activity (*Stokes et al.,*  
235 *2013*), all of which adopted the mean value within a region of interest (ROI), a  
236 lateralization bias toward the right *NAcc* or ventral striatal activation has been  
237 reported. However, such lateralization pattern was not observed in the present  
238 voxel-wise analysis. This is consistent with a voxel-wise heritability approach being  
239 more sensitive in detecting the heredity of brain activation compared with  
240 traditional ROI analysis.

241 It should be noted that only the *NAcc* activation in anticipating monetary gain,  
242 rather than loss, showed significant heritability. This result is consistent with  
243 previous findings reporting significant correlation between *NAcc* activation in older  
244 and younger MZ twins in anticipating monetary gain but not loss (*Silverman et al.,*  
245 *2014*). One possible explanation is that there exists less individual difference in  
246 anticipating monetary gain than loss, even though the *NAcc* activation appears to be  
247 sensitive to both incentive conditions. The small or non-significant heritability could  
248 be attributed to the high phenotypic variance within both MZ and DZ twins due to

249 limited sample size. It is notable that the studies mentioned above only linked  
250 dopaminergic gene polymorphism to ventral striatal activation in processing  
251 monetary gain but not loss, which deserves further investigation.

252 We also investigated the heritability of pleasure experience. In this study, physical  
253 anhedonia traits measured by the RPCAS also demonstrated significant heritability,  
254 whilst experiential pleasure measured by the TEPS was characterized by moderate  
255 but significant heritability. These findings are consistent with previous studies (*Hay*  
256 *et al., 2001; Kendler & Hewitt, 1992; Linney et al., 2003*). In these studies, however,  
257 significant heritability has also been detected in social anhedonia which was not  
258 found in our study. Cultural factors may be a possible influence accounting for this  
259 difference, but this requires further investigation.

260 In the best-fitting genetic model, *NAcc* activation during the anticipation of  
261 monetary gain exhibited significant genetic share with scores on the RPCAS and the  
262 TEPS. In addition, the phenotypic correlation between *NAcc* activation and pleasure  
263 experience was almost entirely attributed to genetic factors. These data suggest that  
264 motivation-related *NAcc* activation during the anticipation of monetary rewards may  
265 share common additive genes with pleasure experience, and these genes contribute  
266 significantly to the phenotypic expression. Locating the shared genes of these two  
267 phenotypes could facilitate clarification of the underlying neurobiological  
268 mechanisms of amotivation and anhedonia in schizophrenia and major depressive  
269 disorder.

270 The main limitation of this study is the modest sample size, which was relatively

271 small for statistical methods applying ACE models. While 196 participants with 174  
272 valid data sets could be regarded as a medium to large sample in task-based fMRI  
273 research, these preliminary results must be replicated in a larger cohort. Importantly,  
274 adopting voxel-wise analysis with correction for multiple comparisons could partially  
275 compensate for the relatively small sample size. One primary problem in genetic  
276 modeling lies in within-group variation, which is sensitive to the presence of outliers;  
277 however, in this study we detected none. Furthermore, demographic variables and  
278 head movements were carefully matched among subgroups with an aim to enhance  
279 the validity of our findings.

280 In conclusion, our findings suggest that motivation-related *NAcc* activation in  
281 anticipating monetary gain and pleasure experience are at least partially heritable.  
282 Importantly, motivation-related *NAcc* activation and pleasure experience exhibit  
283 significant shared genetic covariance. Future molecular studies examining shared  
284 polygenicity of these traits would further inform this research. Locating and refining  
285 areas of the genome associated with expression of these traits will ultimately aid in  
286 the understanding of the underlying neurobiological mechanisms of treatment-  
287 refractory symptoms.

288

## 289 **Materials and methods**

### 290 **Participants**

291 Forty-seven pairs of same-sex dizygotic (DZ) twins and 51 pairs of same-sex  
292 monozygotic (MZ) twins were recruited from the Twin Registry of the Institute of

293 Psychology, the Chinese Academy Sciences (*Chen et al., 2010; Chen et al., 2013*). The  
294 zygosity of each twin was jointly determined by DNA analysis based on saliva, and  
295 two zygosity questionnaires (*Chen et al., 2010*). Potential participants were excluded  
296 from the study if they: 1) had a personal or family history of diagnosable mental  
297 disorders; b) had a history of head trauma or encephalopathy; 3) had a history of  
298 substance abuse, including tobacco and alcohol; 4) had an Intelligence Quotient (IQ)  
299 lower than 70; 5) had severe hearing or visual impairment; or 6) were ambidextrous  
300 or left-handed. This information was verified by the Twin Registry, the participants  
301 themselves, and their guardians. Detailed experimental procedures conformed to  
302 the Declaration of Helsinki and all participants gave written informed consent. All  
303 participants completed checklists capturing experiential pleasure and hedonic traits  
304 before the brain scans. They then undertook the Monetary Incentive Delay (MID)  
305 task inside the scanner. Each participant received 450 RMB as compensation. The  
306 study was approved by the Ethics Committee of the Institute of Psychology, the  
307 Chinese Academy of Sciences.

308

### 309 **Self-report measures of pleasure experience**

310 The revised Chinese versions of the Chapman Physical Anhedonia Scale (RCPAS) and  
311 the Chapman Social Anhedonia Scale (RCSAS) were administered to measure  
312 physical and social anhedonic traits, respectively (*Chan, Wang, et al., 2012*). The  
313 RCPAS consists of 61 true-false items, whereas the RCSAS consists of 40 true-false  
314 items. These two scales have been stable and valid in measuring anhedonic traits

315 across time and along the schizophrenia spectrum (*Chan, Gooding, et al., 2016*). The  
316 Chinese version of the Temporal Experience Pleasure Scale (TEPS) is a 19-item  
317 checklist that was used to measure anticipatory and consummatory pleasure in each  
318 participant (*Chan, Shi, et al., 2012*). The Chinese version has good psychometric  
319 properties for measuring anhedonia across the different stages of schizophrenia  
320 (*Chan et al., 2010; Chan, Shi, et al., 2012; Li et al., 2015*).

321

### 322 **Monetary Incentive Delay (MID) task**

323 We adopted the original version of the MID task developed by Knuston and  
324 colleagues (*Knutson et al., 2000*) to the abridged imaging version (*Chan, Li, et al.,*  
325 *2016*). In each trial of the task, a 250-millisecond cue indicating three different  
326 conditions was first presented at the centre of the screen, followed by a blank  
327 interval that jittered between 2000 and 2500 milliseconds. Then a blue target with  
328 adjusted duration was displayed, followed by an interval that jittered between 500  
329 and 3500 milliseconds. Finally, a 1650-millisecond feedback was presented followed  
330 by an inter-trial interval that jittered between 4000 and 7000 milliseconds. Each trial  
331 lasted 12000 milliseconds (Figure 1A).

332 Participants were asked to hit the target as quickly as possible by pressing the  
333 right button on a panel with their right thumb. The initial duration of the target was  
334 set at 300 milliseconds and changed according to the subsequent performance of  
335 each participant. If a target was successfully hit twice, the target duration was  
336 reduced by 20 milliseconds. Alternatively, if a target was missed twice, 20



337 milliseconds were added to the target duration. Using this strategy, the hit rate of  
338 each participant was controlled at around 66.7%. The three cues indicated three  
339 different conditions: a triangle indicated a monetary gain condition, a square  
340 indicated a monetary loss condition, and a circle indicated a no-incentive condition.  
341 Participants gained five monetary points if they hit the target in the monetary gain  
342 condition, or lost five monetary points if they missed the target in the monetary loss  
343 condition. In the no-incentive condition, participants did not gain or lose any points  
344 whether the target was hit or not. Two runs containing 10 gain, 10 loss and 10 no-  
345 incentive conditions in each run were applied. The trials in each run were presented  
346 in a pseudo-random order. Participants practiced with an independent 30-trial run  
347 before entering the scanner and were informed that their final monetary points  
348 gained in the scanner could be converted into cash and added to their compensation.  
349 This abridged version has been shown to activate the *N*Acc effectively in healthy,  
350 subclinical and clinical samples (*Chan, Li, et al., 2016; Smoski, Rittenberg, & Dichter,*  
351 *2011*).

352

### 353 **Brain image acquisition**

354 Brain imaging data were collected with 32-channel head coil in a 3 T Siemens Trio  
355 MRI Scanner. An experienced radiologist who was blind to this study was responsible  
356 for data acquisition. A T2-weighted FLAIRE sequence (TR = 4000ms; TE = 90ms; FOV =  
357 200mm<sup>2</sup>; slices = 19; flip angle = 120°; image matrix = 256 x 512; voxel dimensions =  
358 0.9 x 0.4 x 5mm<sup>3</sup>) was first used to ascertain that each participant had no organic

359 brain disorders. Then a gradient-echo echo-planner sequence (TR = 2000ms; TE =  
360 30ms; FOV = 210mm<sup>2</sup>; slices = 32; flip angle = 90°; image matrix = 64x64; voxel  
361 dimensions = 3.3 x 3.3 x 4mm<sup>3</sup>; Number of TR = 184 for each run) was applied to  
362 acquire the functional brain activation imaging data of each participant while  
363 performing the MID task. Finally, a high resolution structural brain image was  
364 acquired for anatomical registration (TR = 2300ms; TE = 3ms; FOV = 256mm<sup>2</sup>; flip  
365 angle = 9°; image matrix = 256x256; voxel dimensions = 1 x 1 x 1mm<sup>3</sup>). Each  
366 participant wore earplugs during scanning. Their heads were fixed with a vacuum  
367 pillow and sponge pads to minimize head motion.

368

### 369 **Imaging data processing**

370 The latest version of the SPM 12 (Wellcome Trust Centre for Neuroimaging) was  
371 used for imaging data processing. The functional images were first realigned into the  
372 first volume of each scanning sequence for movement correction, followed by slice  
373 timing correction. The observed head motion parameters, three translations and  
374 three rotations, were calculated into the framewise displacement (FD), a  
375 comprehensive and reliable index for head movement (*Power, Barnes, Snyder,*  
376 *Schlaggar, & Petersen, 2012*). Participants with maximum head motion higher than 2  
377 mm and 2 degrees, and mean FD larger than 0.25 mm were excluded from the final  
378 analysis, along with their twin. Individual high-resolution brain structure image was  
379 non-linearly registered to the Montreal Neurological Institute (MNI) template that  
380 produced a transformation matrix. Using this matrix, all functional brain images were

381 normalized into a common standard atlas. Functional images were resampled into 3  
382  $3 \times 3 \times 3 \text{ mm}^3$  and spatially smoothed with a 6mm full-width-at-half-maximum (FWHM)  
383 Gaussian isotropic kernel. A 128 Hz high-pass filter was applied to the time series of  
384 each voxel to remove low-frequency noise.

385 The preprocessed functional imaging data were included in a first-level general  
386 linear model (GLM) with three predictors of interest during the anticipatory phase  
387 for monetary incentives: gain, loss, and no-incentive. First, the data for each  
388 participant was analyzed to provide a voxel-wise t-statistic map for each contrast,  
389 [gain vs. no-incentive] and [loss vs. no-incentive], during the anticipatory phase. The  
390 time points of target hitting and feedback period were included as parametric  
391 modulation to minimize their influence on the anticipation for incentives. Six raw  
392 head movement parameters were also included as covariates to remove motion  
393 effect. For each contrast, the t-statistics map of all the participants were included  
394 into a GLM with the t-statistics as the dependent variable and the FD as covariate to  
395 further minimize head motion effect. To clarify whether the bilateral *NAcc* were  
396 activated in both MZ and DZ twins, one-sample t-tests were also applied to the t-  
397 statistics of the MZ and DZ groups. The statistical significance threshold of the whole  
398 brain analysis was set as  $p < 0.001$  with FWE correction and cluster voxel size  $> 100$ .  
399 Since 11 pairs of twins were excluded due to excessive head movements, 44 pairs of  
400 DZ twins and 43 pairs of MZ twins were included in the final analysis.

401

402 **Statistical analysis**

403 Pearson chi-square test was used to test if the gender ratio of MZ and DZ twins were  
404 different from each other. The matching of age and years of education between MZ  
405 and DZ twins was tested with independent t-test. Univariate general linear model  
406 with gender, age, and years of education as covariates was used to compare FD,  
407 scores on the RCSAS, the RCPAS, the TEPS and their various subscales between MZ  
408 and DZ twins. The intraclass correlation coefficients (ICC) of behavioral phenotypes  
409 among the MZ and DZ twins were calculated respectively. If the ICC of a phenotype  
410 among MZ twins was significantly twice larger than that for DZ twins, the phenotype  
411 in question may be influenced by familial factors.

412

### 413 **Heritability brain mapping**

414 Voxel-by-voxel heritability brain mapping was carried out with the latest version of  
415 the OpenMx (*Neale et al., 2016*), FSL (*Jenkinson, Beckmann, Behrens, Woolrich, &*  
416 *Smith, 2012*) and in-house MATLAB (The MathWorks, Inc., Natick, Massachusetts,  
417 United States) scripts. Since mapping the heritability of all voxels in the whole brain  
418 may increase the possibility of type II error, we adopted the Oxford-GSK-Imanova  
419 structural striatal atlas which contained the core brain regions sensitive to  
420 dopaminergic activity and reward tasks (*Tziortzi et al., 2011*). The structural striatal  
421 template was first resampled into a 3 x 3 x 3 mm<sup>3</sup> mask containing 765 voxels. The T  
422 values of voxels in the striatal mask were extracted from the two contrast files, [gain  
423 vs. no-incentive] and [loss vs. no-incentive] of each participant. There were no  
424 outliers more than three standard deviations from the mean T value. Age, gender,

425 years of education, and FD were regressed out from the extracted t values to remove  
426 their possible influences on heritability estimation (*Bergen, Gardner, & Kendler, 2007*;  
427 *Lenroot et al., 2009*). Finally, the standardized residuals were submitted to the  
428 genetic model. A conventional univariate ACE model was used, in which A denotes  
429 additive genetic effects, C denotes common environmental effects, and E denotes  
430 unique environmental effects. MZ twins are assumed to share 100 percent of the  
431 additive genetic variance and common environmental variance, whereas the DZ  
432 twins are assumed to share 50 percent of the additive genetic variance and 100  
433 percent of common environmental variance. The part accounted for by A in the total  
434 variance was defined as the heritability estimate  $h^2$  of this phenotype (*Neale & Maes,*  
435 *2004*). To clarify the significance of components A, C and E, sub-models AE and CE  
436 were compared to the full ACE model, and model E was compared to AE and CE  
437 models respectively. If model fit significantly decreased, then the dropped factor was  
438 considered essential in the model. In model selection, the model with the smallest  
439 Akaike's Information Criterion (AIC) value was selected as the best-fit model. We  
440 adopted the  $p$  value of model comparison between the AE and the E model to test  
441 the significance of  $h^2$  if the AE model was detected as the best-fit model the full ACE  
442 model failed to surpass its sub-models in any voxel from the Oxford-GSK-Imanova  
443 structural striatal atlas) (*Neale & Maes, 2004*). Finally, FDR correction with adjusted  $p$   
444  $< 0.05$  was applied to the acquired p-maps to adjust for multiple comparisons.  
445 Comparing to the full ACE model in brain functional or structural studies, the method  
446 in the present study allowed us to quantify the heritability of brain activation and  
447 relevant significance in the best-fit genetic model, and to correct for multiple tests

448 (*Li et al., 2018*). The cluster tool of FSL was used to identify clusters in which  $h^2$  was  
449 significant. Masks with voxels in which the 95% confidence interval of  $h^2$  did not  
450 contain zero were also added onto the brain heritability map.

451

## 452 **Multivariate Model fitting**

453 A trivariate Cholesky ACE model was fitted to examine the genetic sharing between  
454 *NAcc* activation and pleasure experience (RCPAS and TEPS scores) (Figure 2). T values  
455 of the contrast [gain vs. no-incentive] were extracted from bilateral *NAcc* mask with  
456 significant heritability from the heritability brain mapping step. Gender, age, and  
457 years of education were then regressed from the extracted mean T value, RCPAS,  
458 and TEPS scores. The FD value was additionally regressed from the extracted mean T  
459 value for head motion correction. The *NAcc* activation during the anticipation of  
460 monetary loss failed to show significant heritability. In addition, MZ twin correlation  
461 in social anhedonia was not higher than DZ twin correlation and both correlation  
462 coefficients were not significant. Hence, The *NAcc* activation in contrast [loss vs. no-  
463 incentive] and RCSAS were not included in the multivariate genetic model presented  
464 in Figure 2. The trivariate ACE model was first compared with the saturated model in  
465 which all the constraints were set as free. Then the nested sub-models were  
466 compared with the full trivariate ACE model in a stepwise manner. We first  
467 discarded all the model paths containing A, C or E effect in a stepwise manner  
468 (Figure 2 & Table 3). After that we discarded one path from the best fitted model  
469 observed from the above step, and then two paths until the model significantly

470 deteriorated (indicated by  $p < 0.05$ ). The model with the smallest AIC was selected as  
471 the best-fit model, and the likelihood ratio chi-squared statistic, minus two times log  
472 likelihood difference ( $-2LL$ ) were applied for model comparison. The contribution of  
473 A, C, and E to the phenotype correlation between two phenotypes were estimated  
474 using the following formulae:  $r_{ph(g)} = \sqrt{a_{11}^2} * r_g * \sqrt{a_{22}^2}$ ;  $r_{ph(c)} = \sqrt{c_{11}^2} * r_c * \sqrt{c_{22}^2}$ ;  
475  $r_{ph(e)} = \sqrt{e_{11}^2} * r_e * \sqrt{e_{22}^2}$  (Toulopoulou et al., 2015).

476

#### 477 **Acknowledgements**

478 This study was supported by a grant from the Beijing Municipal Science &  
479 Technology Commission Grant (Z161100000216138), National Key Research and  
480 Development Programme (2016YFC0906402), the National Science Fund China  
481 (81571317), the “Strategic Priority Research Programme (B)” of the Chinese  
482 Academy of Sciences (XDB02030002), and the CAS/SAFEA International Partnership  
483 Programme for Creative Research Teams (Y2CX131003). The authors would like to  
484 thank Ting Xu, Qing, Zhao, Chao Yan, Hui-jie Li, Yu-na Wang, Yan-fang Shi, Xiao-yan  
485 Cao, Weizhen Xie, Jie Chen, Xin-ying Li, Jie Zhang and the team members of the  
486 Twins Registry of Institute of Psychology, Chinese Academy Sciences for their kind  
487 recruitment of healthy twins, and all the twin participants for their taking part in the  
488 present study.

489

#### 490 **Author contributions**

491 Zhi Li designed the study, collected and analyzed the data, and wrote up the

492 manuscript. Yi Wang, Chao Yan, Ke Li and Ya-wei Zeng collected all the data and  
493 commented on the first draft of the manuscript. Eric F. C. Cheung, Anna R. Docherty,  
494 Pak C. Sham, Raquel E. Gur and Ruben C. Gur provided significant comments to the  
495 manuscript. Raymond C. K. Chan conceptualized the idea, designed the study,  
496 interpreted the findings and commented the manuscript critically.

497

498 **Additional files**

499 Figure 1 & Table 2 –Source Data 1\_[loss vs. no-incentive]

500 Figure 1 & Table 2 –Source Data 2\_[gain vs. no-incentive]

501 Figure 3-Source Data

502 Figure 4 & Table 3 -Source Data 1

503 Figure 4-& Table 3 Source Data 2

504 Raw data 1\_Activation in each voxel of stritaum\_[loss vs. no-incentive]

505 Raw data 2\_Activation in each voxel of stritaum\_[gain vs. no-incentive]

506 Source Code\_Heritability Brain Mapping 1

507 Source Code\_Heritability Brain Mapping 2

508 Source Code\_Multivariate Model fitting



## 509 **References**

- 510 Aarts, E, Roelofs, A, Franke, B, Rijpkema, M, Fernandez, G, Helmich, RC, & Cools,  
511 R. 2010. Striatal dopamine mediates the interface between motivational and  
512 cognitive control in humans: evidence from genetic imaging.  
513 *Neuropsychopharmacology*, 35(9), 1943-1951. DOI:10.1038/npp.2010.68
- 514 Baldo, BA, & Kelley, AE. 2007. Discrete neurochemical coding of distinguishable  
515 motivational processes: insights from nucleus accumbens control of feeding.  
516 *Psychopharmacology (Berl)*, 191(3), 439-459. DOI:10.1007/s00213-007-  
517 0741-z
- 518 Beck, A, Schlagenhauf, F, Wustenberg, T, Hein, J, Kienast, T, Kahnt, T, Schmack, K,  
519 Hagele, C, Knutson, B, Heinz, A, & Wrase, J. 2009. Ventral Striatal Activation  
520 During Reward Anticipation Correlates with Impulsivity in Alcoholics.  
521 *Biological Psychiatry*, 66(8), 734-742. DOI:10.1016/j.biopsych.2009.04.035
- 522 Bergen, SE, Gardner, CO, & Kendler, KS. 2007. Age-related changes in heritability of  
523 behavioral phenotypes over adolescence and young adulthood: a meta-  
524 analysis. *Twin Res Hum Genet*, 10(3), 423-433. DOI:10.1375/twin.10.3.423
- 525 Berridge, KC. 2003. Pleasures of the brain. *Brain and Cognition*, 52(1), 106-128.  
526 DOI:10.1016/s0278-2626(03)00014-9

- 527 Berridge, KC. 2007. The debate over dopamine's role in reward: the case for  
528 incentive salience. *Psychopharmacology (Berl)*, 191(3), 391-431.  
529 DOI:10.1007/s00213-006-0578-x
- 530 Berridge, KC. 2012. From prediction error to incentive salience: mesolimbic  
531 computation of reward motivation. *European Journal of Neuroscience*, 35(7),  
532 1124-1143. DOI:10.1111/j.1460-9568.2012.07990.x
- 533 Berridge, KC, & Robinson, TE. 1998. Brain Research Reviews. *Brain Res Brain Res*  
534 *Rev*, 28(3), 309-369.
- 535 Bossong, MG, & Kahn, RS. 2016. The Saliency of Reward. *JAMA Psychiatry*, 73(8),  
536 777-778. DOI:10.1001/jamapsychiatry.2016.1134
- 537 Braff, DL, Freedman, R, Schork, NJ, & Gottesman, II. 2007. Deconstructing  
538 schizophrenia: An overview of the use of endophenotypes in order to  
539 understand a complex disorder. *Schizophrenia Bulletin*, 33(1), 21-32.  
540 DOI:10.1093/schbul/sbl049
- 541 Chan, RC, Gooding, DC, Shi, HS, Geng, FL, Xie, DJ, Yang, ZY, Liu, WH, Wang, Y,  
542 Yan, C, Shi, C, Lui, SS, & Cheung, EF. 2016. Evidence of structural  
543 invariance across three groups of Meehlian schizotypes. *NPJ Schizophrenia*,  
544 2, 16016. DOI:10.1038/npjSchz.2016.16

- 545 Chan, RC, Li, Z, Li, K, Zeng, YW, Xie, WZ, Yan, C, Cheung, EF, & Jin, Z. 2016.
- 546 Distinct processing of social and monetary rewards in late adolescents with
- 547 trait anhedonia. *Neuropsychology*, *30*(3), 274-280. DOI:10.1037/neu0000233
- 548 Chan, RC, Wang, Y, Huang, J, Shi, Y, Wang, Y, Hong, X, Ma, Z, Li, Z, Lai, MK, &
- 549 Kring, AM. 2010. Anticipatory and consummatory components of the
- 550 experience of pleasure in schizophrenia: cross-cultural validation and
- 551 extension. *Psychiatry Research*, *175*(1-2), 181-183.
- 552 DOI:10.1016/j.psychres.2009.01.020
- 553 Chan, RCK, Shi, YF, Lai, MK, Wang, YN, Wang, Y, & Kring, AM. 2012. The
- 554 Temporal Experience of Pleasure Scale (TEPS): Exploration and
- 555 Confirmation of Factor Structure in a Healthy Chinese Sample. *Plos One*, *7*(4).
- 556 DOI:10.1371/journal.pone.0035352
- 557 Chan, RCK, Wang, Y, Yan, C, Zhao, Q, McGrath, J, Hsi, XL, & Stone, WS. 2012. A
- 558 Study of Trait Anhedonia in Non-Clinical Chinese Samples: Evidence from the
- 559 Chapman Scales for Physical and Social Anhedonia. *Plos One*, *7*(4).
- 560 DOI:ARTN e3427510.1371/journal.pone.0034275
- 561 Chen, J, Li, X, Chen, Z, Yang, X, Zhang, J, Duan, Q, & Ge, X. 2010. Optimization of
- 562 zygosity determination by questionnaire and DNA genotyping in Chinese

563 adolescent twins. *Twin Research and Human Genetics*, 13(2), 194-200.

564 DOI:10.1375/twin.13.2.194

565 Chen, J, Li, X, Zhang, J, Natsuaki, MN, Leve, LD, Harold, GT, Chen, Z, Yang, X, Guo,

566 F, Zhang, J, & Ge, X. 2013. The Beijing Twin Study (BeTwiSt): a longitudinal

567 study of child and adolescent development. *Twin Research and Human*

568 *Genetics*, 16(1), 91-97. DOI:10.1017/thg.2012.115

569 Craig, W. 1917. Appetites and Aversions as Constituents of Instincts. *Proc Natl Acad*

570 *Sci U S A*, 3(12), 685-688.

571 Cuthbert, BN. 2014. The RDoC framework: facilitating transition from ICD/DSM to

572 dimensional approaches that integrate neuroscience and psychopathology.

573 *World Psychiatry*, 13(1), 28-35. DOI:10.1002/wps.20087

574 Cuthbert, BN, & Insel, TR. 2010. Toward New Approaches to Psychotic Disorders:

575 The NIMH Research Domain Criteria Project. *Schizophrenia Bulletin*, 36(6),

576 1061-1062. DOI:10.1093/schbul/sbq108

577 de Leeuw, M, Kahn, RS, & Vink, M. 2015. Fronto-striatal dysfunction during reward

578 processing in unaffected siblings of schizophrenia patients. *Schizophrenia*

579 *Bulletin*, 41(1), 94-103. DOI:10.1093/schbul/sbu153

580 Docherty, AR, Sponheim, SR, & Kerns, JG. 2015. Self-reported affective traits and

581 current affective experiences of biological relatives of people with  
582 schizophrenia. *Schizophrenia Research*, 161(2-3), 340-344.  
583 DOI:10.1016/j.schres.2014.11.013

584 Dreher, JC, Kohn, P, Kolachana, B, Weinberger, DR, & Berman, KF. 2009. Variation  
585 in dopamine genes influences responsivity of the human reward system. *Proc*  
586 *Natl Acad Sci U S A*, 106(2), 617-622. DOI:10.1073/pnas.0805517106

587 Forbes, EE, Brown, SM, Kimak, M, Ferrell, RE, Manuck, SB, & Hariri, AR. 2009.  
588 Genetic variation in components of dopamine neurotransmission impacts  
589 ventral striatal reactivity associated with impulsivity. *Molecular Psychiatry*,  
590 14(1), 60-70. DOI:10.1038/sj.mp.4002086

591 Gottesman, II, & Gould, TD. 2003. The endophenotype concept in psychiatry:  
592 etymology and strategic intentions. *The American Journal of Psychiatry*,  
593 160(4), 636-645. DOI:10.1176/appi.ajp.160.4.636

594 Grimm, O, Heinz, A, Walter, H, Kirsch, P, Erk, S, Haddad, L, Plichta, MM,  
595 Romanczuk-Seiferth, N, Pohland, L, Mohnke, S, Muhleisen, TW, Mattheisen,  
596 M, Witt, SH, Schafer, A, Cichon, S, Nothen, M, Rietschel, M, Tost, H, &  
597 Meyer-Lindenberg, A. 2014. Striatal response to reward anticipation:  
598 evidence for a systems-level intermediate phenotype for schizophrenia. *JAMA*

- 599            *Psychiatry*, 71(5), 531-539. DOI:10.1001/jamapsychiatry.2014.9
- 600    Haber, SN, & Knutson, B. 2010. The Reward Circuit: Linking Primate Anatomy and  
601            Human        Imaging.        *Neuropsychopharmacology*,        35(1),        4-26.  
602            DOI:10.1038/npp.2009.129
- 603    Hahn, T, Heinzl, S, Dresler, T, Plichta, MM, Renner, TJ, Markulin, F, Jakob, PM,  
604            Lesch, KP, & Fallgatter, AJ. 2011. Association between reward-related  
605            activation in the ventral striatum and trait reward sensitivity is moderated by  
606            dopamine transporter genotype. *Human Brain Mapping*, 32(10), 1557-1565.  
607            DOI:10.1002/hbm.21127
- 608    Hay, DA, Martin, NG, Foley, D, Treloar, SA, Kirk, KM, & Heath, AC. 2001. Phenotypic  
609            and genetic analyses of a short measure of psychosis-proneness in a  
610            largescale Australian twin study. *Twin Research*, 4(1), 30-40.
- 611    Iversen, LL. 2010. *Dopamine handbook*. Oxford ; New York: Oxford University Press.
- 612    Jenkinson, M, Beckmann, CF, Behrens, TE, Woolrich, MW, & Smith, SM. 2012. Fsl.  
613            *Neuroimage*, 62(2), 782-790. DOI:10.1016/j.neuroimage.2011.09.015
- 614    Kendler, KS, & Hewitt, JH. 1992. The structure of self-report schizotypy in twins.  
615            *Journal of Personality Disorders*, 6(1), 1-17.
- 616    Kendler, KS, Thacker, L, & Walsh, D. 1996. Self-report measures of schizotypy as

617 indices of familial vulnerability to schizophrenia. *Schizophrenia Bulletin*, 22(3),

618 511-520.

619 Knutson, B, Bhanji, JP, Cooney, RE, Atlas, LY, & Gotlib, IH. 2008. Neural responses

620 to monetary incentives in major depression. *Biological Psychiatry*, 63(7), 686-

621 692. DOI:10.1016/j.biopsych.2007.07.023

622 Knutson, B, Fong, GW, Adams, CM, Varner, JL, & Hommer, D. 2001. Dissociation of

623 reward anticipation and outcome with event-related fMRI. *Neuroreport*, 12(17),

624 3683-3687. DOI:10.1097/00001756-200112040-00016

625 Knutson, B, & Gibbs, SEB. 2007. Linking nucleus accumbens dopamine and blood

626 oxygenation. *Psychopharmacology*, 191(3), 813-822. DOI:10.1007/s00213-

627 006-0686-7

628 Knutson, B, & Greer, SM. 2008. Anticipatory affect: neural correlates and

629 consequences for choice. *Philosophical Transactions of the Royal Society B-*

630 *Biological Sciences*, 363(1511), 3771-3786. DOI:10.1098/rstb.2008.0155

631 Knutson, B, Westdorp, A, Kaiser, E, & Hommer, D. 2000. FMRI visualization of brain

632 activity during a monetary incentive delay task. *Neuroimage*, 12(1), 20-27.

633 DOI:10.1006/nimg.2000.0593

634 Kring, AM, & Barch, DM. 2014. The motivation and pleasure dimension of negative

635 symptoms: neural substrates and behavioral outputs. *Eur*  
636 *Neuropsychopharmacol*, 24(5), 725-736.  
637 DOI:10.1016/j.euroneuro.2013.06.007

638 Lancaster, TM, Linden, DE, Tansey, KE, Banaschewski, T, Bokde, AL, Bromberg, U,  
639 Buchel, C, Cattrell, A, Conrod, PJ, Flor, H, Frouin, V, Gallinat, J, Garavan, H,  
640 Gowland, P, Heinz, A, Ittermann, B, Martinot, JL, Paillere Martinot, ML,  
641 Artiges, E, Lemaitre, H, Nees, F, Orfanos, DP, Paus, T, Poustka, L, Smolka,  
642 MN, Vetter, NC, Jurk, S, Mennigen, E, Walter, H, Whelan, R, Schumann, G, &  
643 Consortium, I. 2016. Polygenic Risk of Psychosis and Ventral Striatal  
644 Activation During Reward Processing in Healthy Adolescents. *JAMA*  
645 *Psychiatry*, 73(8), 852-861. DOI:10.1001/jamapsychiatry.2016.1135

646 Lenroot, RK, Schmitt, JE, Ordaz, SJ, Wallace, GL, Neale, MC, Lerch, JP, Kendler,  
647 KS, Evans, AC, & Giedd, JN. 2009. Differences in genetic and environmental  
648 influences on the human cerebral cortex associated with development during  
649 childhood and adolescence. *Hum Brain Mapp*, 30(1), 163-174.  
650 DOI:10.1002/hbm.20494

651 Li, Z, Huang, J, Xu, T, Wang, Y, Li, K, Zeng, YW, Lui, SSY, Cheung, EFC, Jin, Z,  
652 Dazzan, P, Glahn, DC, & Chan, RCK. 2018. Neural mechanism and



- 653 heritability of complex motor sequence and audiovisual integration: A healthy  
654 twin study. *Human Brain Mapping*, 39(3), 1438-1448.  
655 DOI:10.1002/hbm.23935
- 656 Li, Z, Lui, SS, Geng, FL, Li, Y, Li, WX, Wang, CY, Tan, SP, Cheung, EF, Kring, AM,  
657 & Chan, RC. 2015. Experiential pleasure deficits in different stages of  
658 schizophrenia. *Schizophrenia Research*, 166(1-3), 98-103.  
659 DOI:10.1016/j.schres.2015.05.041
- 660 Linney, YM, Murray, RM, Peters, ER, MacDonald, AM, Rijdsdijk, F, & Sham, PC. 2003.  
661 A quantitative genetic analysis of schizotypal personality traits. *Psychological  
662 Medicine*, 33(5), 803-816. DOI:10.1017/s0033291703007906
- 663 MacDonald, AW, Pogue-Geile, MF, Debski, TT, & Manuck, S. 2001. Genetic and  
664 environmental influences on schizotypy: A community based twin study.  
665 *Schizophrenia Bulletin*, 27(1), 47-58.
- 666 Meehl, PE. 1975. Hedonic Capacity - Some Conjectures. *Bulletin of the Menninger  
667 Clinic*, 39(4), 295-307.
- 668 Meehl, PE. 1990. Toward an Integrated Theory of Schizotaxia, Schizotypy, and  
669 Schizophrenia. *Journal of Personality Disorders*, 4(1), 1-99.  
670 DOI:10.1521/pedi.1990.4.1.1

- 671 Neale, MC, Hunter, MD, Pritikin, JN, Zahery, M, Brick, TR, Kirkpatrick, RM,  
672 Estabrook, R, Bates, TC, Maes, HH, & Boker, SM. 2016. OpenMx 2.0:  
673 Extended Structural Equation and Statistical Modeling. *Psychometrika*, 81(2),  
674 535-549. DOI:10.1007/s11336-014-9435-8
- 675 Neale, MC, & Maes, HHM. 2004. *Methodology for Genetic Studies of Twins and*  
676 *Families*. Dordrecht, The Netherlands: Kluwer Academic Publishers.
- 677 Nikolova, YS, Ferrell, RE, Manuck, SB, & Hariri, AR. 2011. Multilocus genetic profile  
678 for dopamine signaling predicts ventral striatum reactivity.  
679 *Neuropsychopharmacology*, 36(9), 1940-1947. DOI:10.1038/npp.2011.82
- 680 Oswald, LM, Wong, DF, Zhou, Y, Kumar, A, Brasic, J, Alexander, M, Ye, W,  
681 Kuwabara, H, Hilton, J, & Wand, GS. 2007. Impulsivity and chronic stress are  
682 associated with amphetamine-induced striatal dopamine release. *Neuroimage*,  
683 36(1), 153-166. DOI:10.1016/j.neuroimage.2007.01.055
- 684 Pizzagalli, DA. 2014. Depression, stress, and anhedonia: toward a synthesis and  
685 integrated model. *Annual Review of Clinical Psychology*, 10, 393-423.  
686 DOI:10.1146/annurev-clinpsy-050212-185606
- 687 Pizzagalli, DA, Holmes, AJ, Dillon, DG, Goetz, EL, Birk, JL, Bogdan, R, Dougherty,  
688 DD, Iosifescu, DV, Rauch, SL, & Fava, M. 2009. Reduced Caudate and

689 Nucleus Accumbens Response to Rewards in Unmedicated Individuals With  
690 Major Depressive Disorder. *American Journal of Psychiatry*, 166(6), 702-710.  
691 DOI:10.1176/appi.ajp.2008.08081201

692 Power, JD, Barnes, KA, Snyder, AZ, Schlaggar, BL, & Petersen, SE. 2012. Spurious  
693 but systematic correlations in functional connectivity MRI networks arise from  
694 subject motion. *Neuroimage*, 59(3), 2142-2154.  
695 DOI:10.1016/j.neuroimage.2011.10.018

696 Radua, J, Schmidt, A, Borgwardt, S, Heinz, A, Schlagenhauf, F, McGuire, P, &  
697 Fusar-Poli, P. 2015. Ventral Striatal Activation During Reward Processing in  
698 Psychosis: A Neurofunctional Meta-Analysis. *JAMA Psychiatry*, 72(12), 1243-  
699 1251. DOI:10.1001/jamapsychiatry.2015.2196

700 Silverman, MH, Krueger, RF, Iacono, WG, Malone, SM, Hunt, RH, & Thomas, KM.  
701 2014. Quantifying familial influences on brain activation during the monetary  
702 incentive delay task: an adolescent monozygotic twin study. *Biological*  
703 *Psychology*, 103, 7-14. DOI:10.1016/j.biopsycho.2014.07.016

704 Smoski, MJ, Rittenberg, A, & Dichter, GS. 2011. Major depressive disorder is  
705 characterized by greater reward network activation to monetary than pleasant  
706 image rewards. *Psychiatry Research*, 194(3), 263-270.

- 707 DOI:10.1016/j.psychoresns.2011.06.012
- 708 Stokes, PR, Shotbolt, P, Mehta, MA, Turkheimer, E, Benecke, A, Copeland, C,  
709 Turkheimer, FE, Lingford-Hughes, AR, & Howes, OD. 2013. Nature or nurture?  
710 Determining the heritability of human striatal dopamine function: an [18F]-  
711 DOPA PET study. *Neuropsychopharmacology*, 38(3), 485-491.  
712 DOI:10.1038/npp.2012.207
- 713 Touloupoulou, T, van Haren, N, Zhang, X, Sham, PC, Cherny, SS, Campbell, DD,  
714 Picchioni, M, Murray, R, Boomsma, DI, Pol, HH, Brouwer, R, Schnack, H,  
715 Fananas, L, Sauer, H, Nenadic, I, Weisbrod, M, Cannon, TD, & Kahn, RS.  
716 2015. Reciprocal causation models of cognitive vs volumetric cerebral  
717 intermediate phenotypes for schizophrenia in a pan-European twin cohort.  
718 *Molecular Psychiatry*, 20(11), 1482. DOI:10.1038/mp.2015.117
- 719 Tziortzi, AC, Searle, GE, Tzimopoulou, S, Salinas, C, Beaver, JD, Jenkinson, M,  
720 Laruelle, M, Rabiner, EA, & Gunn, RN. 2011. Imaging dopamine receptors in  
721 humans with [11C]-(+)-PHNO: dissection of D3 signal and anatomy.  
722 *Neuroimage*, 54(1), 264-277. DOI:10.1016/j.neuroimage.2010.06.044
- 723 Vignapiano, A, Mucci, A, Ford, J, Montefusco, V, Plescia, GM, Bucci, P, & Galderisi,  
724 S. 2016. Reward anticipation and trait anhedonia: An electrophysiological

- 725 investigation in subjects with schizophrenia. *Clinical Neurophysiology*, *127*(4),  
726 2149-2160. DOI:10.1016/j.clinph.2016.01.006
- 727 Vink, M, de Leeuw, M, Pouwels, R, van den Munkhof, HE, Kahn, RS, & Hillegers, M.  
728 2016. Diminishing striatal activation across adolescent development during  
729 reward anticipation in offspring of schizophrenia patients. *Schizophrenia*  
730 *Research*, *170*(1), 73-79. DOI:10.1016/j.schres.2015.11.018
- 731 Wacker, J, Dillon, DG, & Pizzagalli, DA. 2009. The role of the nucleus accumbens  
732 and rostral anterior cingulate cortex in anhedonia: integration of resting EEG,  
733 fMRI, and volumetric techniques. *Neuroimage*, *46*(1), 327-337.  
734 DOI:10.1016/j.neuroimage.2009.01.058
- 735 Wrase, J, Schlagenhauf, F, Kienast, T, Wustenberg, T, Bermanpohl, F, Kahnt, T, Beek,  
736 A, Strohle, A, Juckel, G, Knutson, B, & Heinz, A. 2007. Dysfunction of reward  
737 processing correlates with alcohol craving in detoxified alcoholics.  
738 *Neuroimage*, *35*(2), 787-794. DOI:10.1016/j.neuroimage.2006.11.043
- 739 Yacubian, J, Sommer, T, Schroeder, K, Glascher, J, Kalisch, R, Leuenberger, B,  
740 Braus, DF, & Buchel, C. 2007. Gene-gene interaction associated with neural  
741 reward sensitivity. *Proc Natl Acad Sci U S A*, *104*(19), 8125-8130.  
742 DOI:10.1073/pnas.0702029104

743

744 Table1. Demographics of participants

	MZ (N = 86)	ICC	DZ (N = 88)	ICC	$\chi^2/t/F$	p	ALL (N = 174)
Gender (Male/Female)	46/40	/	46/42	/	0.026	0.872	92/82
Age	19.98(1.89)	/	19.8(1.76)	/	-0.66	0.513	19.89(1.82)
Education	12.33(1.75)	0.671**	12.44(1.63)	0.591**	0.46	0.647	12.39(1.69)
FD	0.13(0.04)	0.204	0.13(0.04)	-0.059	0.156	0.694	0.13(0.04)
RCSAS	11.38(5.96)	0.087	7.57(4.48)	0.281	22.38	< 0.001**	9.45(5.59)
RCPAS	22.12(8.03)	0.490**	18.97(7.66)	0.201	6.29	0.013*	20.52(7.98)
TEPS	4.06(0.59)	0.352*	4.08(0.59)	-0.02	0.004	0.947	4.07(0.59)
TEPS_Anticipation	4.11(0.67)	0.396**	4.13(0.7)	-0.021	0.19	0.662	4.12(0.68)
TEPS_Consummation	4.11(0.77)	0.346*	4.12(0.75)	0	0.19	0.667	4.14(0.76)

745 Note: \*, p < 0.01; \*\*, p < 0.05; MZ = Monozygotic twins; DZ = Dizygotic twins; ICC = Interclass correlation coefficient; FD = Frame Displacement; RCSAS =  
 746 Revised Chapman Social Anhedonia Scale; RCPAS = Revised Chapman Physical Anhedonia Scale; TEPS = Temporal Experience Pleasure Scale.

747

748 Table2. Whole brain activation in anticipating monetary incentive

Region(L/R)	MZ (N = 86)		DZ (N = 88)		ALL (N = 174)	
	T	Peak Coord.	T	Peak Coord.	T	Peak Coord.
Gain vs. No-incentive						
NAcc (R)	12.1	[6,9,3]	13.41	[-12,6,-6]	16.73	[6,9,0]
NAcc (L)	11.27	[-6,6,0]	12.38	[9,9,-3]	16.63	[-9,6,-3]
Thalamus					14.16	[0,-9,3]
Insula (L)	10.52	[-27,27,3]				
Insula (R)			10.26	[33,24,3]		
Loss vs. No-incentive						
NAcc (R)	10.7	[0,-6,0]	12.22	[-12,6,-9]	15.18	[9,3,-3]
NAcc (L)	10.4	[6,6,0]	11.73	[9,3,-3]	15.01	[-9,3,0]
Thalamus					13.99	[0,-6,0]
Thalamus (R)			11.32	[12,-3,6]		
Globus pallidus (L)	10.36	[-9,3,0]				

749 Note: All the results were corrected with FEW method,  $p < 0.001$ , cluster voxel size  $> 100$ ;  
750 MZ = Monozygotic twins; DZ = Dizygotic twins; L = Left; R = Right; Coord. = Coordinate; NAcc  
751 = Nucleus Accumbens.

752



753 Table3. Model fitting and selection

No.	Model	ep	-2LL	df	AIC	diffLL	diffdf	<i>p</i>
I	Saturated Model	54	1342.45	468	406.45	/	/	/
	<b>Cholesky Trivariate Model</b>	<b>21</b>	<b>1384.4</b>	<b>501</b>	<b>382.4</b>	<b>41.94</b>	<b>33</b>	<b>0.14</b>
II	Drop a or c matrix							
III	<b>Drop c matrix</b>	<b>15</b>	<b>1384.65</b>	<b>507</b>	<b>370.65</b>	<b>0.25</b>	<b>6</b>	<b>1</b>
IV	Drop a matrix	15	1396.98	507	382.98	12.59	6	0.05
	Drop one path based on the model III							
V	Drop a31	14	1387.21	508	371.21	2.56	1	0.11
VI	Drop a32	14	1387.68	508	371.68	3.03	1	0.08
VII	Drop a21	14	1390.61	508	374.61	5.95	1	0.01
VIII	Drop e32	14	1390.07	508	374.07	5.42	1	0.02
IX	Drop e31	14	1385.22	508	369.22	0.57	1	0.45
X	<b>Drop e21</b>	<b>14</b>	<b>1384.66</b>	508	368.66	0.01	1	0.94
	Drop two paths based on the model X							
XI	Drop e21 and a31	13	1387.37	509	369.37	2.71	1	0.1
XII	Drop e21 and a32	13	1388.4	509	370.4	3.75	1	0.05
XIII	Drop e21 and a21	13	1393.18	509	375.18	8.53	1	0
XIV	Drop e21 and e32	13	1390.07	509	372.07	5.42	1	0.02
XV	<b>Drop e21 and e31</b>	<b>13</b>	<b>1385.35</b>	<b>509</b>	<b>367.35</b>	<b>0.69</b>	<b>1</b>	<b>0.4</b>
	Drop three paths based on the model XV							
XVI	Drop e21 and e31 and a31	12	1393.29	510	373.29	7.94	1	0
XVII	Drop e21 and e31 and a21	12	1394.03	510	374.03	8.68	1	0
XVIII	Drop e21 and e31 and a32	12	1388.44	510	368.44	3.09	1	0.08
XIX	Drop e21 and e31 and e32	12	1390.56	510	370.56	5.21	1	0.02

754 Note: No. = Model number; Model = Parameters drop by this model; ep = estimate parameter; -2LL = minus 2 log  
755 likelihood; df = degree of freedom; AIC = Akaike information criterion; diffLL = the difference of minus 2 log  
756 likelihood between two models; diffdf = the difference of the degree of freedom between two models; *p* indicates  
757 the significance of model deterioration between two models. The trivariate genetic model was compared with the  
758 saturated model first, then the sub-models II – IV were compared with the full genetic model from which the model  
759 III was selected as the best-fitted model for the next step parameter dropping. One parameter was first drop from  
760 the model III in which the model X was selected. Then two parameters were drop based on the model X. Finally, the  
761 model XV with the smallest AIC among all tested sub-models was chosen as the best fitted model, which model did  
762 not deteriorate by compared with the model X (*p* > 0.05).

763

764 **Legends**

765 **Figure1. Monetary incentive delay (MID) task and brain activation in anticipating**  
766 **monetary gain and loss.** A: The Workflow of one trial in the MID task; B: The  
767 activation of bilateral nucleus accumbens (*NAcc*) was found in contrast [Gain vs. no-  
768 incentive] during the anticipatory phase, the white-red color bar indicates the  
769 statistical t value; C: The activation of bilateral *NAcc* was found in contrast [Loss vs.  
770 no-incentive] during the anticipatory phase, the white-blue color bar indicates the  
771 statistical t value.

772

773 **Figure2. Full trivariate genetic model with Cholesky decomposition.** The *NAcc*  
774 indicates the extracted t value from the contrast file of [Gain vs. No-incentive], with  
775 the mask from the voxel-wise heritability mapping of brain activation. The RPCAS  
776 indicates the physical anhedonia trait, whilst the TEPS indicates the experiential  
777 pleasure. The A indicates the additive genetic effect, the C indicates the common  
778 environmental effect, and the E indicates the unique environmental effect. The  
779 lowercase with number indicates the path of model, such as 'a21' indicates the  
780 influence from the additive gene effect of *NAcc* to RPCAS.

781

782 **Figure3. Voxel-wise heritability mapping on brain activation.** In the standard  
783 striatum atlas on the right, two clusters with significant heritability in bilateral *NAcc*  
784 are detected, which ranges from 0.2 to 0.49 in each voxel (reflected by the white-red  
785 color bar). The five pie charts on the left indicate the heritability and unique

786 environmental effect of AE model on the two clusters, in which the golden color  
787 indicates the heritability whilst the blue color indicates the unique environmental  
788 effect.

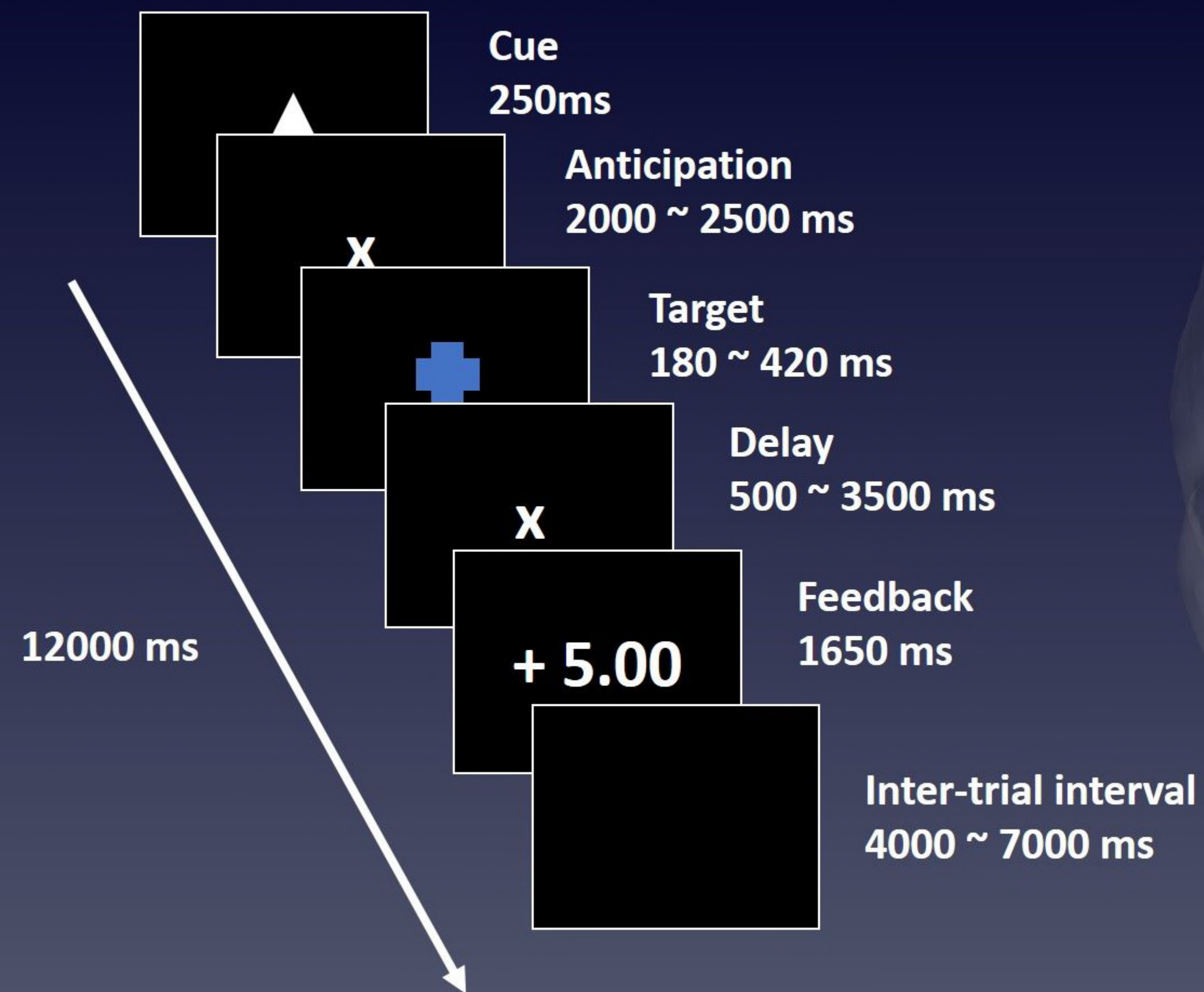
789

790 **Figure4. The best-fitted trivariate genetic model.** Only the additive genetic and  
791 unique environmental effects contribute to this model. The  $h^2$  indicates the  
792 heritability with 95% confidence interval of each single phenotype, the  $r_{ph}$  indicates  
793 the phenotypic correlation between phenotypes, the  $r_g$  indicates the genetic  
794 correlation, and the  $r_e$  indicates the unique environmental correlation. The  $r_{ph(g)}$  and  
795  $r_{ph(e)}$  indicates the contributions to phenotypic correlation, from the additive gene  
796 and unique environment respectively. The standard path coefficients with 95%  
797 confidence interval were also supplied in this figure.

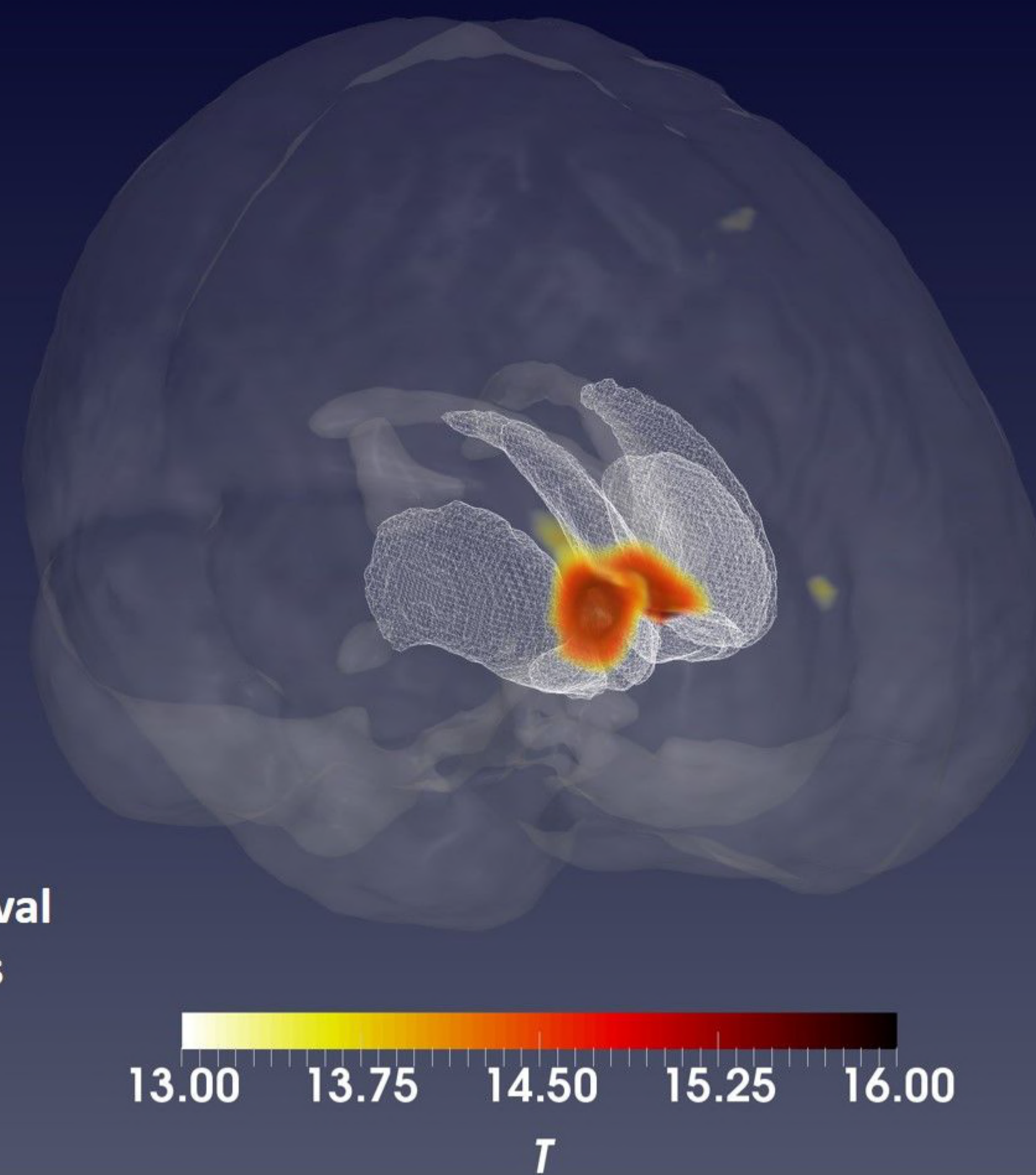
798

799

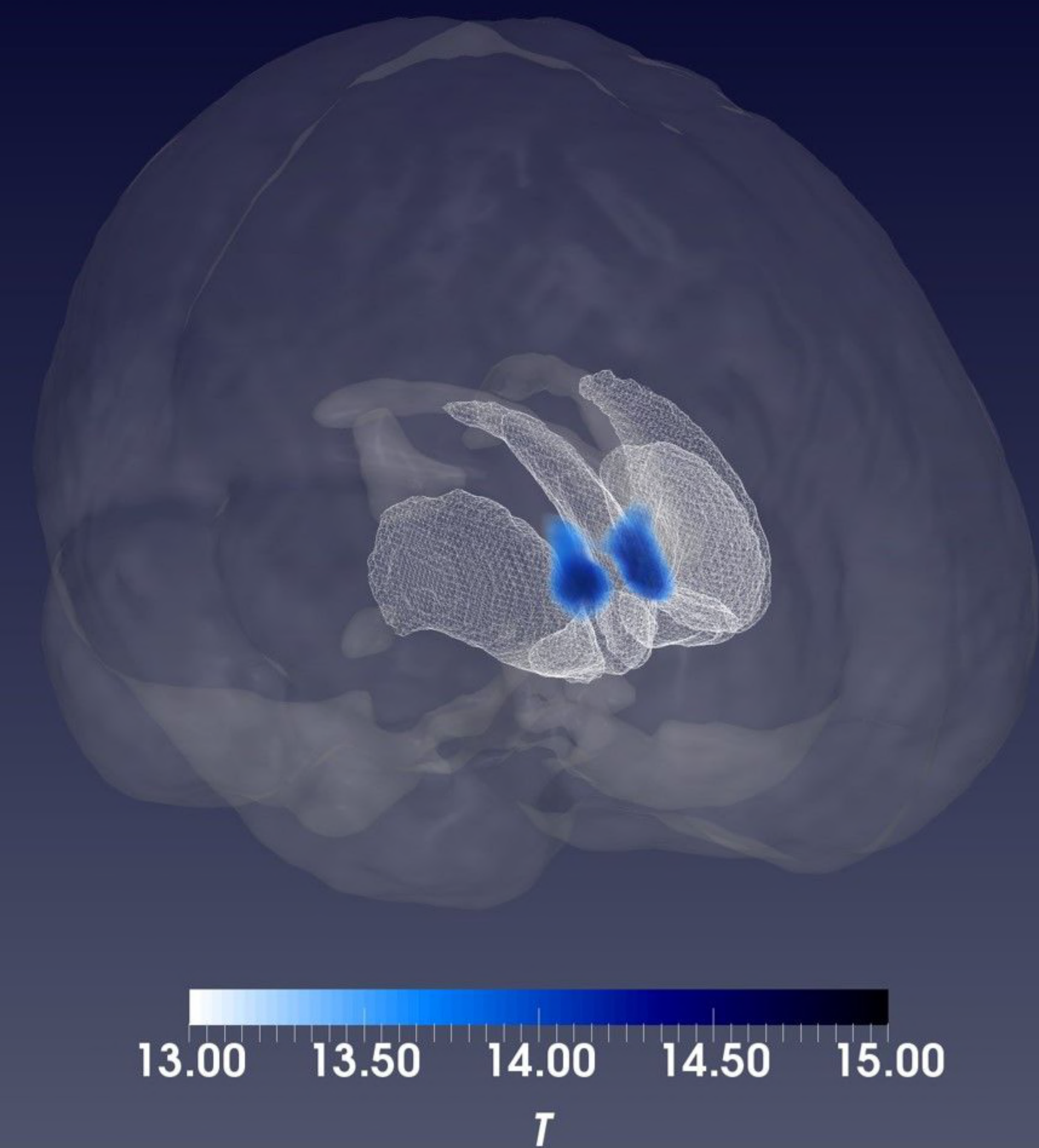
## A. Procedure of One trial

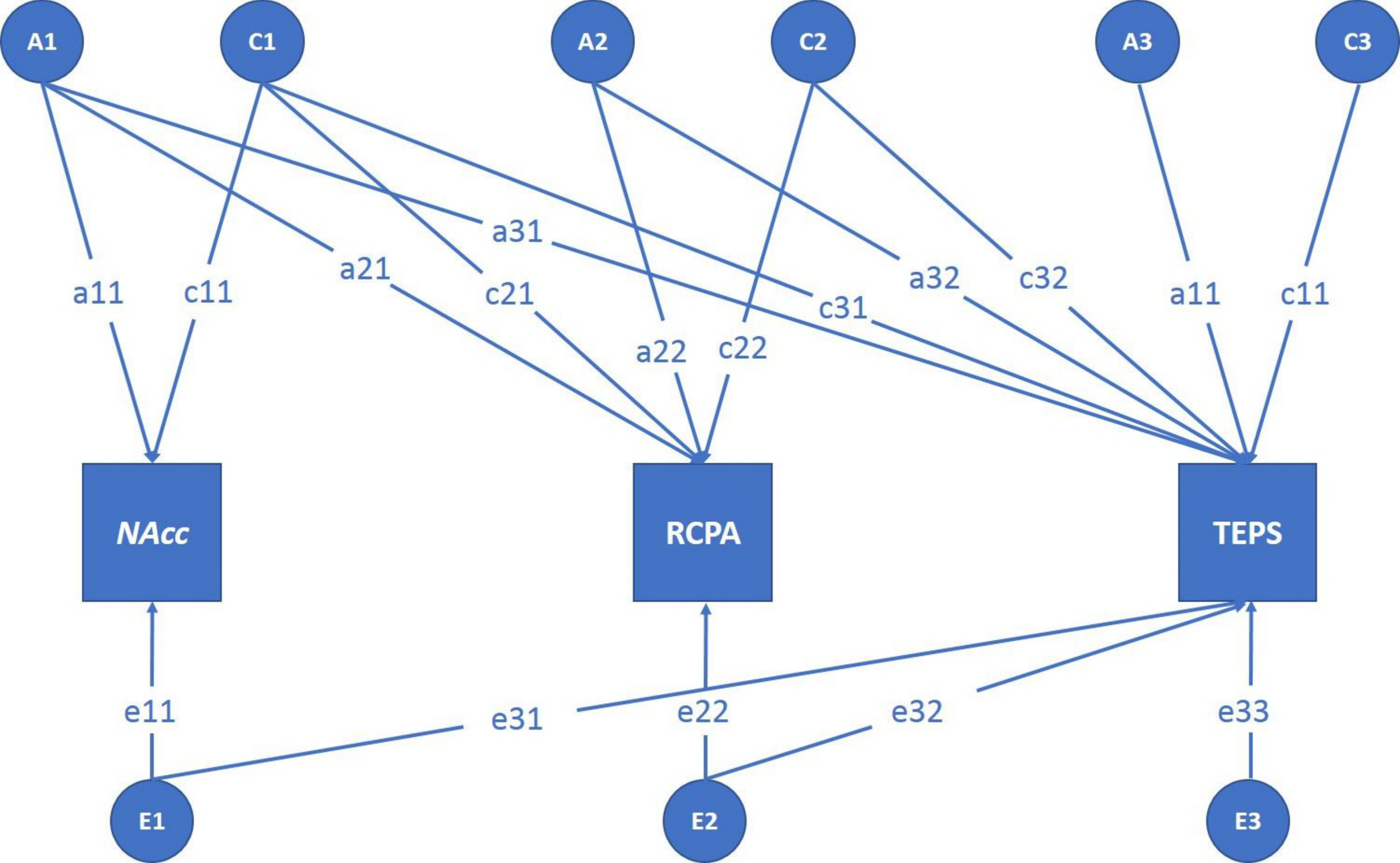


## B. Gain vs. No-incentive

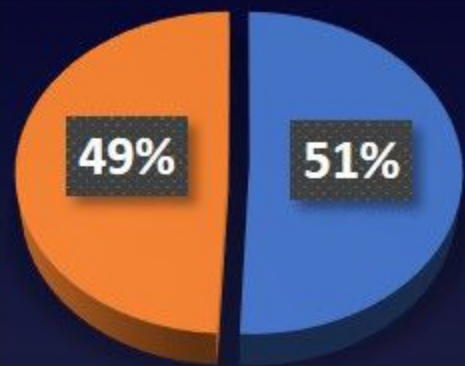


## C. Loss vs. No-incentive

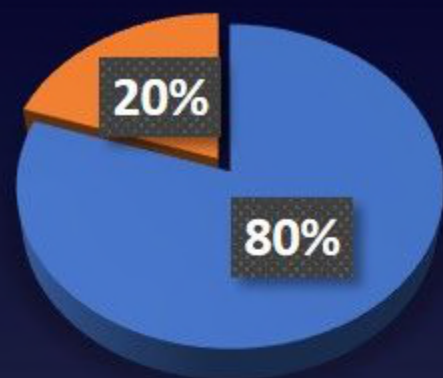




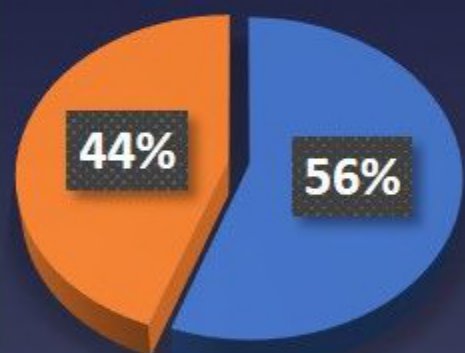
A. Max  $h^2$  vs. Min  $e^2$



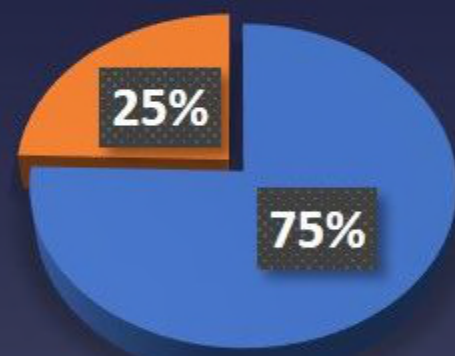
B. Min  $h^2$  vs. Max  $e^2$



C. Left peak point



D. Right peak point



E. Mean  $h^2$  vs.  $e^2$

