

Dopamine modulates the neural representation of subjective value of food in hungry subjects

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2 **hungry subjects**

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82 **Abstract**

83 While there is a rich literature on the role of dopamine in value learning, much less is known
84 about its role in using established value estimations to shape decision-making. Here we
85 investigated the effect of dopaminergic modulation on value-based decision-making for food
86 items in fasted healthy human participants. The Becker-deGroot-Marschak auction, which
87 assesses subjective value, was examined in conjunction with pharmacological functional
88 magnetic resonance imaging (fMRI) using a dopaminergic agonist and an antagonist. We found
89 that dopamine enhanced the neural response to value in the inferior parietal
90 gyrus/intraparietal sulcus, and that this effect predominated towards the end of the valuation
91 process when an action was needed to record the value. Our results suggest that dopamine is
92 involved in acting upon the decision, providing additional insight to the mechanisms underlying
93 impaired decision-making in healthy individuals and clinical populations with reduced
94 dopamine levels.

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96 **Introduction**

97 Successful interactions with the environment – those that maximise reward and minimise
98 punishment – entail using previous experience to predict the likely value of outcomes and the
99 actions that obtain them. Animal and human studies have strongly implicated the
100 neurotransmitter dopamine in this value learning process (Bayer and Glimcher, 2005; Schultz,
101 1998; Schultz et al., 1997; Steinberg et al., 2013; Wise, 2004; Frank and O’Reilly, 2006; Frank et
102 al., 2004; Pessiglione et al., 2006), in addition to its other overlapping roles in shaping
103 behaviour, including motivation (Berridge and Robinson, 1998), vigour (Niv et al., 2007) and
104 behavioural activation (Robbins and Everitt, 2007).

105 But choice requires not merely an ability to predict the consequences of one’s actions. One must
106 be able to weigh up the likely values of competing possibilities. Thus, it is critical to retrieve and
107 represent the subjective values of the options on offer in order to select the most valuable one.
108 This value computation – an intrinsic part of decision-making - has been linked to the function
109 of certain key brain regions in humans and non-human primates, including the ventromedial
110 prefrontal cortex (vmPFC), ventral striatum, posterior parietal and supplementary motor cortex
111 (Bartra et al., 2013; Clithero and Rangel, 2013; Hunt et al., 2012; O’Doherty, 2011; Platt and
112 Glimcher, 1999; Wunderlich et al., 2009). The key question posed in the current study is
113 whether value-related processes in these regions may be modulated by dopamine.

114 Single cell recordings from dopamine neurons responding to reward-predicting stimuli have
115 implicated dopamine in the neural coding of the subjective value of stimuli (Fiorillo et al., 2003;
116 Roesch et al., 2007; Tobler et al., 2005). Furthermore, recent pharmacological studies suggested
117 a role of dopamine in the optimal selection of most valuable stimuli within probabilistic learning
118 tasks (Jocham et al., 2011; Shiner et al., 2012; Smittenaar et al., 2012). However, there is a
119 critical distinction between value updating (learning) and value-based decision-making, and
120 these cannot be fully dissociated within probabilistic learning tasks. Whereas both processes
121 are hypothesised to be modulated by dopamine (McClure et al., 2003), the distinct role of

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122 dopamine in decision-making, dissociated from learning, has not been experimentally
123 investigated. To address this, we conducted a between-subject, placebo-controlled
124 pharmacological fMRI study in healthy volunteers.

125 We explored the effects of both a dopamine agonist and an antagonist on the subjective
126 valuation of food items in a Becker-deGroot-Marschak (BDM) mechanism (Becker et al., 1964).
127 The BDM replicates many aspects of second-price auctions and provides a robust means of
128 obtaining subjective values and involves no learning component. It has been used in human
129 neuroscience before (Grether et al., 2007; Plassmann et al., 2007). All items in the auction were
130 well-known everyday foods whose value subjects would have acquired through life experience,
131 independent of our experimental manipulation. This enabled us to characterise the impact of
132 dopaminergic modulation on the behavioural and brain processes associated primarily with
133 decision-making.

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135 **Materials and methods**

136 **Subjects**

137 Forty-seven healthy, right-handed people (23 males, aged 23.8 ± 3.2 , body mass index 21.7 ± 1.6
138 kg/m^2 (mean \pm SD)) participated in the study. All subjects had normal or corrected to normal
139 vision, had no history of psychiatric or other significant medical history, and reported no
140 contraindications to the pharmacological agents or MRI scanning.

141 The study was approved by the Cambridge East Local Research Ethics Committee (REC
142 11/EE/0480) and was conducted at the Wellcome Trust Clinical Research Facility and the
143 Wolfson Brain Imaging Centre in Addenbrooke's Hospital, Cambridge, UK. The study was
144 carried out in accordance with the principles of the Declaration of Helsinki. All participants
145 provided written, informed consent.

146 **Study design**

147 In a double-blind, between-subject study, subjects received a single oral dose of either
148 bromocriptine 1.25 mg (dopamine D2 agonist, $n=15$), sulpiride 400 mg (D2 antagonist, $n=16$) or
149 placebo ($n=16$). One subject (from the sulpiride group) did not pay attention to the task and was
150 excluded from the analysis (on over 50% of the free trials, the subject placed a bid of £0; when
151 debriefed, she did not express any dislike of the food items on offer or a desire to keep her
152 budget, thus calling into question her understanding of the task). Three additional subjects (one
153 from each group) were excluded from the fMRI analysis because of severe signal dropout in the
154 frontal lobe, as agreed on visual inspection by the study analysis team. This left 46 datasets (23
155 males, aged 23.8 ± 3.2 , body mass index $21.7 \pm 1.6 \text{ kg/m}^2$ (mean \pm SD)) for the behavioural analysis
156 and 43 datasets (21 males, aged 23.6 ± 2.9 , body mass index $21.5 \pm 1.5 \text{ kg/m}^2$ (mean \pm SD)) for the
157 fMRI analysis. Subjects' age ($F = 0.45$, $p = 0.64$), BMI ($F = 1.02$, $p = 0.37$) or gender ($\chi^2 = 0.04$, $p =$
158 0.98) did not differ between the treatment groups. In addition to the task described below,
159 participants underwent a number of other cognitive measures, which are not presented here.

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160 Subjects attended the study session in the morning following an overnight fast. They received a
161 standardised breakfast (based on body weight, age and gender) on the clinical research facility
162 at 8am. This was to ensure similar baseline metabolic states across subjects and to minimise
163 pharmacokinetic perturbations related to food and drink.

164 Bromocriptine and sulpiride have been used in previous studies (Cools et al., 2009; Dodds et al.,
165 2009; Morcom et al., 2010), and are well tolerated at these doses. As bromocriptine can cause
166 nausea (Bromocriptine SPC, 2012), to maintain the double-blinding and prevent any effects of
167 nausea on performance on a food-related task, all subjects were prophylactically given 10 mg of
168 the anti-emetic domperidone, which does not cross the blood-brain barrier (Domperidone SPC,
169 2012). Bromocriptine reaches peak plasma levels 1-3 hours post dose, with a half-life of about
170 15 hours (Kvernmo et al., 2006). Sulpiride reaches its maximal plasma concentration about 3
171 hours post dose, and has a plasma half-life of about 12 hours (Caley and Weber, 1995; Wiesel et
172 al., 1980). The study drug and domperidone were given to all participants at 11am. The fMRI
173 acquisition started approximately 2.5 hours after receiving the drugs (at ~1:30 pm) to capture
174 the window of maximal drug effect.

fMRI task

176 A computerised version of the BDM auction was developed, in which participants could bid for
177 50 different foods, represented by photographs (see Figure 1A). Participants were given a fixed
178 budget, and the auction procedure incentivises participants to place bids as close as possible to
179 their real subjective value.

180 In addition to their study participation fee, before entering the scanner, participants were
181 handed a budget of £3 for bidding. This was physically given to them to ensure they regarded
182 the budget as their own money. They were instructed that on each trial they could place a bid
183 between £0 and £3 for the presented item. Responses were made on a sliding scale that went
184 from £0 to £3 in increments of 20 pence. Participants were told that the computer would bid
185 against them on each trial but the bid would not be disclosed to them. As per the rules of the

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186 auction, one trial would be randomly selected at the end of the auction (subjects therefore did
187 not have to spread their £3 budget across different trials, and were instructed to treat every
188 trial as if it were the only one). If their bid for the food item on the selected trial was larger than
189 the computer's, they would win that food item, get a chance to eat it after the scanning session
190 and only have to pay the amount the computer bid (which would be less than their bid) and
191 keep any remaining change. If, however, the computer outbid them or matched their bid, they
192 would not win the food item but would get to keep their £3 budget. Given this set-up, the
193 auction is incentive-compatible, i.e. the best strategy is to place a bid close to what one is
194 actually willing to pay. As the actual amount paid is determined by the computer's bid on the
195 selected trial, bidding higher amounts risks having to pay more than one's subjective value.
196 Bidding lower amounts runs the risk of losing the opportunity to win the item (more cheaply
197 than one was prepared to pay for it). These rules were all explicitly stated and emphasised to
198 the subjects as part of the task instructions. Critically, participants were in a hungry state and
199 were told that they could eat any food they won after the scanning session.

200 Since each trial entails a number of perceptuomotor components, we used an approach taken by
201 Plassmann et al., (2007), by including a control task in which the same 50 foods were presented
202 in "forced" trials (as opposed to the above "free" trials) where subjects were instructed to bid an
203 amount taken from a random distribution of possible bids from £0 to £3 pounds, again in 20
204 pence increments. These trials required participants to engage in all the processes involved in
205 the free trials with the critical difference of requiring no subjective valuation. Moreover,
206 participants were aware that they would not lose money on such trials.

207 Fifty trials of each trial type (free and forced), of duration 8 seconds, were presented in a
208 randomised order. The picture of the food was presented throughout the entire 8-second
209 duration of a trial. The initial position of the cursor on the sliding scale varied randomly.
210 Participants placed bids using a standard button box with the first and second buttons serving
211 to move the cursor down or up the sliding value scale in steps of 20 pence, and the third button

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212 serving to confirm the final bid and mark the end of the bidding. From this point until the end of
213 the 8-second bidding trial, the cursor could not be moved further. When the 8-second bidding
214 trial was over, a feedback screen showing the final bid was presented (Figure 1A). If the bid was
215 not confirmed within 8 seconds, the feedback screen stated “Not quick enough”. In the analysis,
216 these trials were considered missed trials.

217 In fact, for practical reasons, the task was set up to ensure that subjects did not win a food item,
218 but instead ended up keeping their £3 budget.

219 Behavioural analysis

220 Behavioural data were analysed using mixed-effects models (nlme package in R (Pinheiro et al.,
221 2013)), with subjects as a random effect. Post-hoc comparisons, where needed, were done using
222 the multcomp package (Hothorn et al., 2008).

223 fMRI data acquisition and analysis

224 All data were acquired on a Siemens Verio scanner operating at 3 Tesla with a 192mm field of
225 view at the Wolfson Brain Imaging Centre, Cambridge, UK. A total of 570 gradient echo T2*-
226 weighted echo planar images (EPI) depicting blood oxygenation level dependent (BOLD)
227 contrast were acquired for each participant. The first six images were discarded to avoid T1
228 equilibration effects. Images comprised 31 slices, each 3mm thick with a 0.8mm inter-slice gap
229 and a 64 × 64 data matrix. Slices were acquired in an ascending interleaved fashion, repetition
230 time = 2000ms, echo time = 30ms, flip angle = 78°, axial orientation = oblique. Data were
231 analysed using statistical parametric mapping in the SPM8 program (www.fil.ion.ucl.ac.uk).
232 Images were realigned then spatially normalised to a standard template and spatially smoothed
233 with an isotropic 3 dimensional Gaussian filter (8 mm full width at half maximum). The time
234 series in each session were high-pass filtered (with cut-off frequency 1/120 Hz) and serial
235 autocorrelations were estimated using an AR(1) model.

236

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237 *Model 1: Brain responses to value across the entire bidding period and its modulation by* **238 *dopamine***

239 Each bidding trial was modelled as a boxcar function, from the onset of the food stimulus until
240 the bid was confirmed (duration equal to RT, Figure 1B). Separate regressors were created for
241 free and forced trials. Free and forced bids were used as parametric modulators of these
242 regressors. Missed trials (in which no bids were selected within 8 seconds) were modelled as a
243 separate regressor. All regressors were convolved with a canonical haemodynamic response
244 function with a temporal derivative. Six motion realignment parameters were included as
245 regressors of no interest.

246 To examine processes specifically associated with valuation, we calculated the first-level
247 contrasts as the difference between the parametric modulator of free bid in free trials and
248 forced bid in forced trials. Given that in forced trials subjects implemented instructed bids, these
249 trials should not engage the circuitry of interest to us but they should engage all other non-
250 specific processes related to valuation. The applied contrast thus corrects for non-specific
251 effects and enables identification of regions specifically involved in the valuation-based decision
252 process. Single-subject contrast images were then entered into a second-level group analysis,
253 with subjects as a random effect.

254 At the second level, two analyses were performed:

255 1. To explore which brain regions are involved in valuation across all subjects, independent of
256 pharmacological treatment, we computed a one-sample t-test on the single-subject contrast
257 coefficients from all 43 participants. The analysis was conducted within a pre-defined 10mm
258 radius sphere in the vmPFC (from the work of Chib et al. (2009)), with a family-wise error
259 (FWE) small-volume corrected threshold of $p < 0.05$. This was based on our a priori hypothesis
260 given the strong evidence implicating this region in value computation. In addition, we explored
261 the existence of value related signals across the whole brain, adopting a threshold of $p < 0.05$,

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262 FWE corrected at the cluster-level. Additionally, for completeness, we explored the existence of
263 brain regions whose neural activity separately correlated with free bids in free trials and forced
264 bids in forced trials. We also explored whether there was a region whose activity tracked the
265 mismatch between free bid and the randomly ascribed forced bid for the same food item during
266 forced trials; this entailed examining the existence of correlation between neural activity during
267 forced trials and a parametric modulator of the difference between the free bid and the randomly
268 ascribed forced bid for same food item. These additional analyses were conducted at the whole-
269 brain level, using a more liberal threshold of $p < 0.001$, uncorrected.

270 2. To explore the effect of the dopaminergic modulation on the neural representation of value,
271 we performed a non-directional F-test (ANOVA). This was again conducted within the vmPFC
272 ROI, applying a small-volume corrected threshold of $p < 0.05$, and at the whole-brain level, at a
273 more liberal threshold of $p < 0.001$ uncorrected, $k > 20$ voxels. This threshold at the whole-brain
274 level was adopted because it is not possible to apply a cluster-level correction for F-tests in
275 SPM8 and a voxel-level correction would be too stringent. In case of significant effects, they
276 were further delineated using two-sample t-tests at the whole-brain cluster-level and within the
277 vmPFC sphere, at a FWE corrected threshold of $p < 0.05$.

278

Model 2: Does dopamine have different contributions to different phases of the bidding/valuation process?

281 This post-hoc analysis aimed to establish the temporal specificity of the dopaminergic effects
282 and, in so doing, to relate them to the early (initial valuation) and late (value-dependent action)
283 stages of the bidding process. A modified first-level model was estimated that looked for
284 changes in the correlation of BOLD activity with the bid separately for early and late phases of
285 each trial.

286

287 To model the early and late stages of the bidding process, two regressors were created for each

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288 subject. These two regressors were modelled as 0s stick functions: an early period regressor
289 was set at the time of food photo (and trial) onset, and a late period regressor was set at a time
290 half-way from the food photo onset to the bid confirmation (RT/2). This was done separately
291 for each trial (Figure 1C). Whereas at the first time point no responding took place, at the
292 second time point, participants were responding to select the bid. Missed early and late
293 regressors were modelled as separate 0s stick functions, with the late time point regressor
294 modelled at 4s (halfway through the trial). The parametric modulators of bids for early and late
295 time points were the same for a given trial. To identify neural representations of value at each
296 time point, two separate single-subject contrasts were computed: the early neural
297 representation of value as the difference between the parametric modulator of free bid and
298 forced bid at the early time point; and the late neural representation as the difference between
299 the parametric modulator of free bid and forced bid at the late time point.

300

301 The two contrast images per each individual were put forward to the second-level group
302 analysis, with subjects as a random effect. At the group level we used a 2x3 factorial ANOVA to
303 explore the interaction between time and drug on the neural representation of value. This
304 analysis was confined to a 10mm-radius sphere around the peak voxel exhibiting the strongest
305 dopaminergic modulation of neural representation of value, established in the previous
306 analysis. The analysis was conducted at a FWE small-volume corrected threshold of $p < 0.05$.

307

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308 **Results**

309 **Behavioural results**

310 ***Missed trials***

311 Predictably, there were significantly fewer missed trials within the free than in the forced trials
312 (free (mean±SEM): 0.48± 0.12, forced (mean±SEM): 1.52± 0.27, $F=17.49$, $p=0.0001$), however
313 this did not differ across groups (trial type-by-group interaction $F=0.14$, $p=0.87$).

314 ***Bid***

315 Despite a clear trend for higher free bids in the sulpiride group (Figure 2A), the effect of
316 treatment did not reach significance ($F=2.83$, $p=0.07$). Pairwise comparisons revealed a
317 strongest difference between sulpiride and bromocriptine, however this did not reach
318 significance (sulpiride versus bromocriptine, $z=2.16$; $p=0.08$, placebo versus bromocriptine
319 $z=0.23$, $p=0.97$; sulpiride versus placebo $z=1.96$, $p=0.12$, Tukey-corrected for multiple
320 comparisons).

321 Free bids were found to be positively correlated with the initial random position of cursor on
322 the bidding scale ($t=6.09$, $p<0.0001$), however, this did not differ between different treatment
323 groups (initial cursor position-by-treatment group interaction $F=1.76$, $p=0.17$). Adding the
324 initial cursor position as the covariate into the model exploring the effect of treatment group on
325 the bid did not change the reported results.

326 ***Reaction time***

327 Individual reaction times (RTs) were, of course, dependent on the initial position of the cursor
328 since this would determine how far they were required to move in order to finalise the
329 selection. There was thus a correlation between starting point and RT ($t=10.15$, $p<0.0001$). To
330 account for this, the number of button presses made to select the bid was entered as a covariate
331 into the model exploring the effect of trial type and drug treatment on RT. The analysis revealed

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332 a significant effect of trial type ($F=398.39$, $p<0.0001$), with subjects, as expected, being quicker
333 on forced compared to free trials (Figure 2B). There was no main effect of treatment ($F=1.01$,
334 $p=0.37$), however there was a significant treatment-by-trial type interaction ($F=3.7$, $p=0.025$).
335 None of the pairwise comparisons between drug treatments in the free condition reached
336 significance, however, as evident from the plot, there was a trend of shorter RTs under sulpiride
337 in comparison to placebo and bromocriptine (placebo versus bromocriptine $z=0.47$, $p=0.86$;
338 sulpiride versus bromocriptine $z=-1.29$, $p=0.39$; sulpiride versus placebo $z=-1.78$, $p=0.18$;
339 Tukey corrected for multiple comparisons). As evident from the plot, the analogous analysis
340 within the forced trials revealed no difference in reaction RTs between drug treatments
341 (placebo versus bromocriptine $z=-0.46$, $p=0.89$; sulpiride versus bromocriptine $z=-0.85$, $p=0.67$;
342 sulpiride versus placebo $z=-0.41$, $p=0.91$; Tukey corrected for multiple comparisons).

fMRI results

344 As described above, two key analyses were performed. Our first analysis treated the entire
345 duration of the bidding (equal to RT, mean $RT\pm SD = 4.1\pm 1.37s$) as the period of interest to
346 identify regions sensitive to value and dopaminergic modulation (Model 1, Figure 1B). Next we
347 sought to determine whether in these regions, there were differential effects of dopamine on
348 different aspects of the bidding process (Model 2, Figure 1C). Model 2 examined whether the
349 drug effects were specific to a particular stage of each trial. Dividing every trial into early and
350 late phases (corresponding approximately to initial valuation and value-dependent action) on
351 the basis of the response made, we explored the interaction between drug, value (bid size) and
352 trial phase (early versus late).

353

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357 *The neural representation of value (Model 1)*

358 Examination of the brain regions involved in valuation across all study participants revealed
359 activity correlating with subjective value within the pre-defined region of vmPFC ($p_{FWE}<0.05$,
360 small volume corrected, Figure 3A), consistent with theory and previous work (Bartra et al.,
361 2013; Clithero and Rangel, 2013). Further, several clusters were seen (whole-brain cluster-level
362 $p_{FWE}<0.05$) including a large cluster encompassing the left and right posterior parietal cortex
363 (maxima located in the region of intraparietal sulcus (IPS) on both sides) and extending to the
364 left fusiform gyrus and further clusters in middle and inferior frontal gyri bilaterally and in the
365 right fusiform/lingual gyrus (Figure 3B and Table 1).

366 For completeness, we conducted two additional analyses. Firstly, we explored the correlation of
367 neural activity with free and forced bids separately. Whereas the neural activity correlating with
368 free bids in free trials mimicked the pattern of neural activity in our main contrast, there was no
369 region, even at a liberal threshold of $p<0.001$ uncorrected, whose activity correlated with forced
370 bids in forced trials. This confirms that the effects established in our main contrast were not
371 driven by activity associated with forced trials. Secondly, we also investigated whether there
372 was a region whose activity tracked the mismatch between free bid and the randomly ascribed
373 forced bid for the same food item during forced trials. That is, we determined whether being
374 forced to make a bid that markedly deviated from how one would normally value a given item
375 was associated with enhanced responses. However, no such region was detected, even at a
376 liberal threshold of $p<0.001$ uncorrected.

377 *Dopaminergic drugs modulate the neural response to value in the left and right inferior* 378 ***parietal gyrus/intraparietal sulcus (Model 1)***

379 We next explored the effect of the administered dopaminergic drugs on the valuation-
380 dependent brain activity. The ANOVA comprising the three levels of pharmacological treatment
381 found no effect of treatment in the vmPFC (this was also true for a more liberal threshold,

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382 $p < 0.001$ uncorrected). A significant effect of dopaminergic treatment was found in the right
383 middle frontal gyrus and in the left and right inferior parietal gyrus, in close vicinity of the IPS
384 (IPG/IPS; $p < 0.001$ uncorrected, $k > 20$ voxels; Table 2, Figure 4A).

385 To establish more precisely what drove this effect, additional two-sample t-tests were
386 performed. Compared to sulpiride, bromocriptine was associated with a stronger relationship
387 between value and activity in the IPG/IPS bilaterally (corrected for multiple comparisons at the
388 cluster-level, $p_{FWE} < 0.05$, Table 3, Figures 4B and 4D); in other words, it increased the strength of
389 correlation between the bids and the BOLD response. Further t-tests between individual
390 pharmacological treatments did not reveal any significant clusters at the same threshold.

391 Interestingly, these two clusters were close to the posterior parietal cluster identified in the
392 previous contrast. As can be seen from the parameter estimates (Figure 4C), there was a trend
393 towards reduced neural representation of value within the sulpiride group in the posterior
394 parietal cluster, however, the clear distinction between the groups was only seen in the L- and
395 R-IPG/IPS clusters.

396 In summary, we found that the neural response to value is significantly affected by
397 pharmacological manipulation of dopaminergic function in the IPG/IPS region and this effect
398 was driven by the bromocriptine versus sulpiride contrast.

Dopaminergic treatment modulates the neural representation of value in the left inferior parietal gyrus/intraparietal sulcus during the late stage of valuation (Model 2)

401 Here, we investigated whether the dopaminergic modulation is specific to the early or late stage
402 of the valuation process. We focused specifically on the regions showing an effect of drug across
403 the whole trial, splitting this trial into early and late phases (with the split-point determined
404 based on time-to-decision for each trial separately). A significant time-by-drug interaction was
405 established in a 10mm-radius sphere around the peak voxel in the left IPG/IPS demonstrating
406 the strongest effect of dopaminergic treatment in the previous model ($p_{FWE} < 0.05$, small volume

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407 corrected, Table 4, Figure 5A). As evident from the parameter estimates extracted from each of
408 six conditions (Figure 5B), the effect of dopaminergic manipulation on valuation was greater
409 during the later (value-dependent action) phase compared to the earlier (initial valuation)
410 phase. This result suggests that the modulation of strength of correlation between the bids and
411 the BOLD signal in the left IPG/IPS, increasing with bromocriptine and decreasing with
412 sulpiride, becomes more pronounced closer to the point when an appropriate action is used to
413 record the final bid, i.e. when the participant makes a fine-grained decision about whether the
414 bid should be 20p more or less, which in the context of our task might indicate a dopaminergic
415 influence on the fine tuning of the valuation process.

416

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417 **Discussion**

418 In this pharmacological fMRI study we used the established BDM mechanism with food rewards,
419 in a sample of hungry participants, to assess the role of dopamine in subjective valuation. We
420 characterised the effects of dopaminergic modulation, using both an agonist and an antagonist,
421 demonstrating its role in the coding of value in the IPS. Compared to sulpiride, bromocriptine
422 enhanced the neural representation of value in the IPS. Moreover, a significant drug-by-value-
423 by-trial phase interaction indicated that the dopaminergic modulation of neural response was
424 specific to the late phase of the trials, when an action was needed to record the value.

425

426 While there is a rich literature on the role of dopamine in value learning (Bayer and Glimcher,
427 2005; Schultz, 1998; Schultz et al., 1997; Steinberg et al., 2013; Wise, 2004), there is relatively
428 little exploring its role in value computation during decision-making. Recent studies in healthy
429 adults and patients with Parkinson's disease have partly addressed this using a probabilistic
430 learning/choice task, demonstrating that dopamine biases choice towards more valuable
431 options (Jocham et al., 2011; Shiner et al., 2012; Smittenaar et al., 2012) and enhances the
432 expression of value in the vmPFC (Jocham et al., 2011). However, the learning nature of these
433 tasks prevents a clear dissociation of dopaminergic effects on learning and performance/choice
434 (particularly given that in Jocham et al. (2011) the dopamine-modulated prediction error
435 expressed during the learning phase also predicted choice in the performance phase). Our
436 results concur with these findings, and complement them by demonstrating a dopaminergic
437 component of value computation in response to already well-learned items. Furthermore, the
438 realistic nature of the task and the inclusion of highly-familiar foods as auction items more
439 closely mimics every day value computations we make, which, compared to choosing between
440 probabilistic stimulus-reward associations, are more complex and are thought to entail
441 integration of various attributes into a single measure of subjective value, which can be then
442 used as input for making choices (Rangel et al., 2008).

443

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444 Interestingly, while our first analysis (“Model 1”) replicated previous work in showing value
445 signals in several brain regions including vmPFC (Bartra et al., 2013; Clithero and Rangel, 2013;
446 Hunt et al., 2012; O’Doherty, 2011), only in the IPS was value representation modulated by
447 dopamine. The finding of a dopaminergic effect in the IPS and not in the vmPFC, and the
448 relatively late timing of this signal, suggests that a different, dopamine-sensitive value
449 computation is being processed in the IPS. We are cautious about interpreting a null effect in
450 vmPFC but it is worth noting that the association of BOLD activity in this region with value has
451 been generally established at the initial stages of the decision-making process and is thought to
452 serve as an input to later stages of decision-making (Rangel, 2010; Rangel and Clithero, 2013).
453 Conversely, posterior parietal cortex has been implicated as central to action-based decision-
454 making (Dorris and Glimcher, 2004; Musallam et al., 2004; Platt and Glimcher, 1999; Sugrue et
455 al., 2004). Notably, one part of this region, the lateral intraparietal area has been found to
456 represent a spatial map for guiding saccades (Snyder et al., 1997), and to encode the value of
457 rewards associated with individual saccades (Dorris and Glimcher, 2004; Platt and Glimcher,
458 1999; Sugrue et al., 2004). The parietal reach region analogously represents the movement of
459 forelimbs (Baumann et al., 2009; Connolly et al., 2003; Scherberger and Andersen, 2007), and
460 the firing of these neurons correlates with the expected value of the movement’s outcome
461 (Musallam et al., 2004). These findings suggest that these two areas encode the value of
462 movements. Human studies have also related measures of action value to activity in the
463 IPS/posterior parietal cortex (Chowdhury et al., 2013; Gershman et al., 2009; Hunt et al., 2012;
464 Iyer et al., 2010; Wunderlich et al., 2009).

465 One possibility is that dopaminergic enhancement of the neural representation of value reflects
466 an increase in the signal to noise ratio (SNR) of the value representation. Evidence for this
467 comes from studies of the decline in dopamine function with aging (reviewed in Bäckman et al.,
468 (2006)). Neural network simulations modelling age-related decline in dopaminergic function as
469 attenuated gain control of SNR (Eppinger et al., 2011; Li et al., 2001) have suggested a plausible
470 mechanistic link between reduced dopaminergic function, attenuated neural representation of

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471 the value of stimuli and impairments in decision-making. Furthermore, studies in older adults
472 demonstrated that the increased BOLD signal temporal variability (Samanez-Larkin et al.,
473 2010a) and reduced neural representation of expected value (Samanez-Larkin et al., 2010b)
474 were predictive of poorer decision-making. Our results complement these findings by directly
475 showing the effects of dopaminergic modulation on the neural representation of value.
476 Moreover, the fact that the drug modulations occurred late in the trials (i.e. close to the final
477 selection of the bid) suggests that dopamine modulates the dynamic process of fine tuning the
478 neural representation of value as the basis for completing the decision/action.

479 Behaviourally, we did not detect an effect of dopaminergic treatment on the magnitude of bids,
480 perhaps as consequence of the relatively mild pharmacological perturbation induced. However,
481 the presence of significant neural alterations in the context of matched behaviour offers some
482 advantages to interpreting the former more clearly, in keeping with previous theoretical
483 perspectives (Wilkinson and Halligan, 2004). Moreover, to the best of our knowledge, there is
484 no data demonstrating that dopamine increases value in a context dissociated from learning. A
485 more detailed analysis of the RTs revealed that the average time to decide on the size of the bid
486 was reduced in the sulpiride condition, suggestive of decreased deliberation on the value of
487 individual foods. Interestingly, this effect was paralleled by a trend towards larger bids in the
488 sulpiride condition. In fact, the average bid under sulpiride is much closer to the mean bid in the
489 forced condition (see Figure 2A). Given that the bids in the forced condition were taken from a
490 random, uniform distribution, we speculate that sulpiride, and the proposed decrease in SNR of
491 value representation, were associated with more random, less deliberative bids.

492

493 Finally, it is noteworthy that part of the posterior parietal region lying in close proximity to the
494 dopamine-dependent value coding region identified in this study has been found to be related to
495 goal-directed behaviour (Glascher et al., 2010). Given that dopamine has been implicated in
496 mediating the balance between the habitual and goal-directed systems, with increased
497 dopaminergic activity shifting the behaviour towards a more dominant goal-directed control

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498 (de Wit et al., 2011, 2012; Wunderlich et al., 2012), and given the importance of valuation in
499 goal-directed behaviour, we speculate that our agonist and antagonist drugs shifted this balance
500 in different directions with the former promoting more measured, goal-directed responding and
501 the latter, through reducing value SNR, prompting more rapid responses divorced from goal
502 values. Of course, this is a speculation and our experimental design does not allow us to test it
503 directly.

504 Certain limitations must be acknowledged. The between-subject design prevented analyses of
505 potential brain-behaviour correlations. Further, while pharmacological fMRI is widely used and
506 provides a targeted, non-invasive way of investigating neural processes, there are some basic
507 limitations of the approach. Given the limited data on dose and receptor occupancy
508 relationships for these agents, doses and administration protocols are based on the known
509 pharmacokinetics of these drugs and on previous studies that have successfully used them to
510 perturb dopaminergic function (Cools et al., 2009; Dodds et al., 2009; Mehta et al., 2008;
511 Morcom et al., 2010). Dosages are also limited by what can be deemed clinically tolerable for
512 healthy volunteers. Furthermore, there are studies reporting effects different from our findings
513 – namely, enhanced neural value representation and improvement in performance associated
514 with D2 antagonists, presumably linked to pre-synaptic auto-receptors effects (Jocham et al.,
515 2011; Frank and O'Reilly, 2006). The preponderance of post- versus pre-synaptic effects is
516 believed to vary depending on the exact drug used, its concentration, the basal level of
517 dopamine in the system (discussed in Frank and O'Reilly (2006)), as well as on the brain area of
518 the studied effect, given the different distribution of post- and pre-synaptic receptors
519 throughout the brain (Kilts et al., 1987). It is not possible to entirely exclude the possibility of
520 auto-receptors effects in our study though the directionality of our effects does instil some
521 confidence that we are seeing predominantly post-synaptic effects.

522 In summary, we explored the role of dopamine in the neural representation of value without the
523 confound of learning. We investigated the direct role of dopamine in the expression of value that

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524 has been already learned through life experience, and whose accurate expression is a requisite
525 of goal-directed behaviour. Our results suggest that dopamine enhances the neural
526 representation of value in the IPS. The effect predominates towards the end of the valuation
527 process, at the point where the decision becomes explicit in action. These findings provide a
528 dopamine-dependent mechanism underlying impaired decision-making in healthy individuals
529 and clinical populations with reduced dopamine levels.

530

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670 **Figure legends**

671 **Figure 1. Task structure and model specification.**

672 A. The auction task featured 50 snack items presented as part of free and forced trials. Free and
673 forced trials, of duration 8s, were presented in a randomised order. After the bidding trial was
674 over, a 1s feedback screen showing the final bid was presented. This was followed by a 0.5s
675 blank screen. On 30 random occasions during the course of the task, a 6s null trial with a
676 fixation cross was presented after the blank screen.

677 B. fMRI model 1 schematic. Each bidding trial was modelled as a boxcar function (depicted as a
678 pink rectangle), from the onset of the food stimulus until the bid was confirmed (duration equal
679 to RT).

680 C. fMRI model 2 schematic. Two time points within each bidding trial were modelled as events
681 within the trial (0s stick or delta functions, depicted as pink rectangles): an early phase
682 regressor set at the time of food stimulus onset, and a late phase regressor set at a time half-way
683 from the food photo onset to the bid confirmation ($RT/2$), separately for each trial.

684 **Figure 2. Behavioural results.**

685 A. Average bid by treatment group in the free trial condition. Error bars represent SEM of each
686 subject's average bid. Presented on the same graph is the mean of the uniform distribution of
687 instructed forced bids.

688 B. Average RT by treatment group and trial type. Error bars represent SEM of each subject's
689 average RT.

690

691

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692 Figure 3. Neural representation of value.

693 Significant areas of activation were rendered onto a standard SPM8 T1 template image, with
694 coronal and sagittal sections presented at the coordinates appropriate for displaying relevant
695 regions.

696 A. The neural representation of value was found within the pre-defined 10mm-radius sphere in
697 the vmPFC region ($p_{FWE} < 0.05$, small-volume corrected).

698 B. Equally, value-coding clusters were found in regions surviving the whole-brain correction at
699 the cluster-level ($p_{FWE} < 0.05$). These include a large cluster encompassing the left and right
700 posterior parietal cortex (maxima located in the region of IPS on both sides) and extending to
701 the left fusiform gyrus and further clusters in middle and inferior frontal gyri bilaterally and in
702 the right fusiform / lingual gyrus.

703 Full details of the activation foci are given in Table 1.

704 Figure 4. Dopaminergic modulation of the neural representation of value.

705 Significant areas of activation were rendered onto the standard SPM8 T1 template image, with
706 coronal and sagittal sections presented at the coordinates appropriate for displaying relevant
707 regions.

708 A. Activation areas in the left and right IPG/IPS and in the right middle frontal gyrus that
709 exhibited an effect of drug on the neural representation of value ($p < 0.001$ uncorrected, $k > 20$
710 voxels).

711 B. Displayed in green are the activation areas in the left and right IPG/IPS in which there was an
712 enhancement of the neural representation of value in the bromocriptine compared to the
713 sulpiride treatment group ($p_{FWE} < 0.05$, whole-brain corrected at the cluster-level). Value-coding

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714 clusters, common to all three treatment groups, are presented in magenta ($p_{FWE} < 0.05$, whole-
715 brain corrected at the cluster-level).

716 C. Presented inside the magenta box are the parameter estimates of the neural representation of
717 value averaged per treatment groups, extracted from the large value-coding cluster spanning
718 the left and right posterior parietal cortex (presented in magenta on the images in panel B).

719 D. Presented inside the green box are the parameter estimates of the neural representation of
720 value averaged per treatment groups, extracted from the left and right IPG/IPS clusters of the
721 bromocriptine versus sulpiride contrast (presented in green on the images in panel B).

722 Error bars represent SEM. Full details of the activation foci are given in Tables 2 and 3.

723 Figure 5. Dopaminergic treatment modulates the neural representation of value in the 724 left inferior parietal gyrus/intraparietal sulcus during the late stage of valuation.

725 Coronal (at $y = -54$ mm to the anterior commissure) and sagittal sections (at $x = -54$ mm to the left
726 of the mid-line) from the standard SPM8 T1 template image.

727 A. The analysis was confined to a 10mm-radius sphere around the voxel in the left IPG/IPS that
728 showed the strongest dopamine-dependent modulation in model 1, and is depicted here in
729 green. Presented in yellow are the voxels within this sphere showing a significant treatment
730 (placebo, bromocriptine, sulpiride) by time (early, late) interaction. For display purposes, both
731 contrasts are presented at $p < 0.01$ uncorrected.

732 B. Presented inside the yellow box are the parameter estimates of the neural representation of
733 value for each of the six conditions: treatment (placebo/bromocriptine/sulpiride) and time
734 (early/late). The parameter estimates were extracted from the voxels exhibiting the treatment-
735 by-time interaction within the described sphere (presented in yellow on the image in panel A).

736 Error bars represent SEM. Full details of the activation foci are given in Table 4.

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737 **Table legends**

738 **Table 1.** Regions correlated with subjective value.

739 **Table 2.** Regions exhibiting a dopaminergic modulation of the neural representation of value.

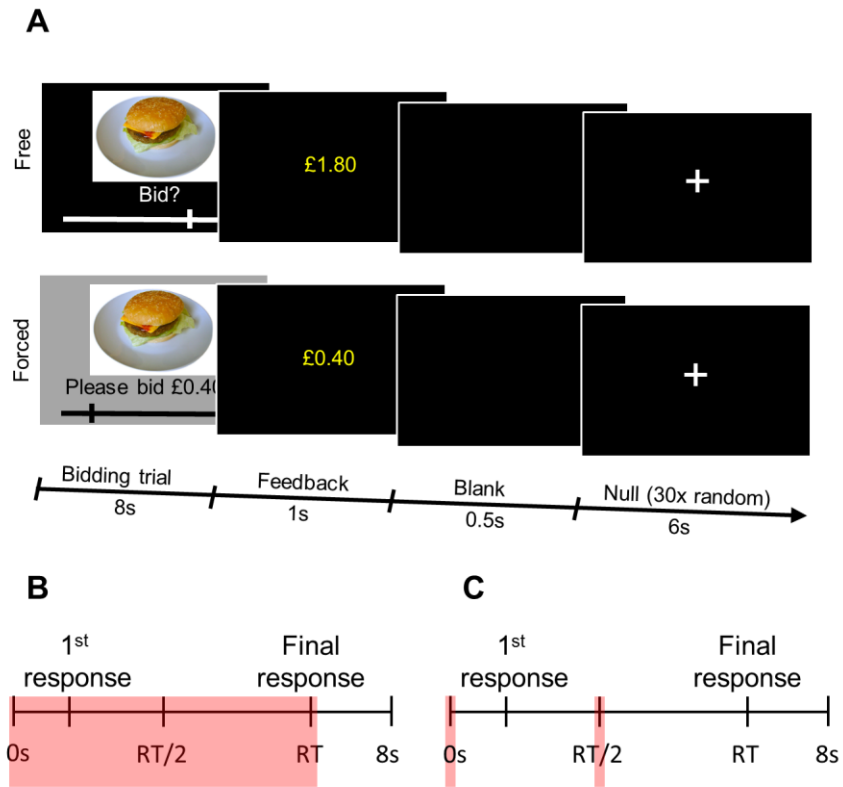
740 **Table 3.** Regions with an enhanced neural representation of value under bromocriptine,
741 compared to sulpiride.

742 **Table 4.** Activation peak exhibiting a time-by-treatment interaction in the left IPG/IPS.

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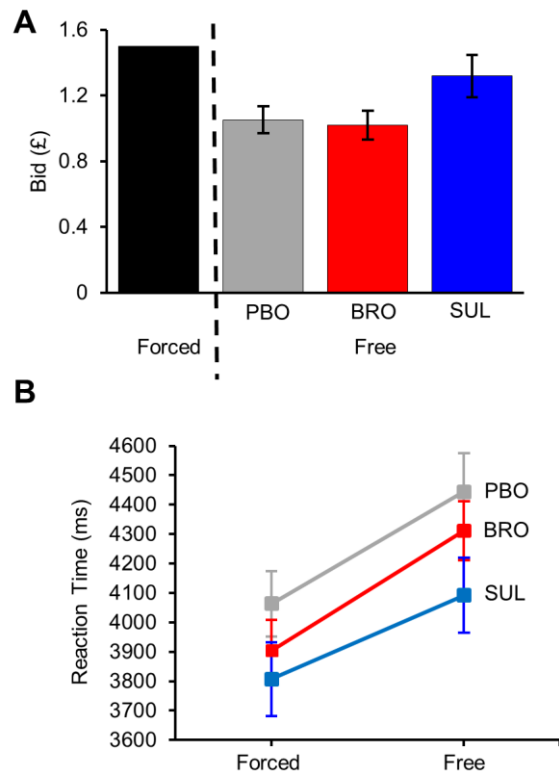
Figures

Figure 1



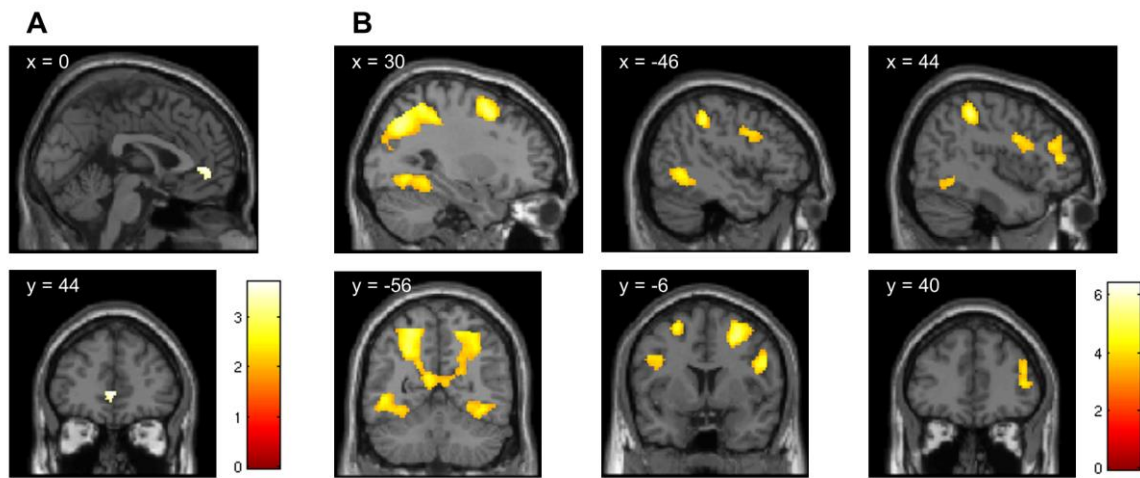
Dopamine modulates the neural representation of subjective value of food in hungry subjects

Figure 2



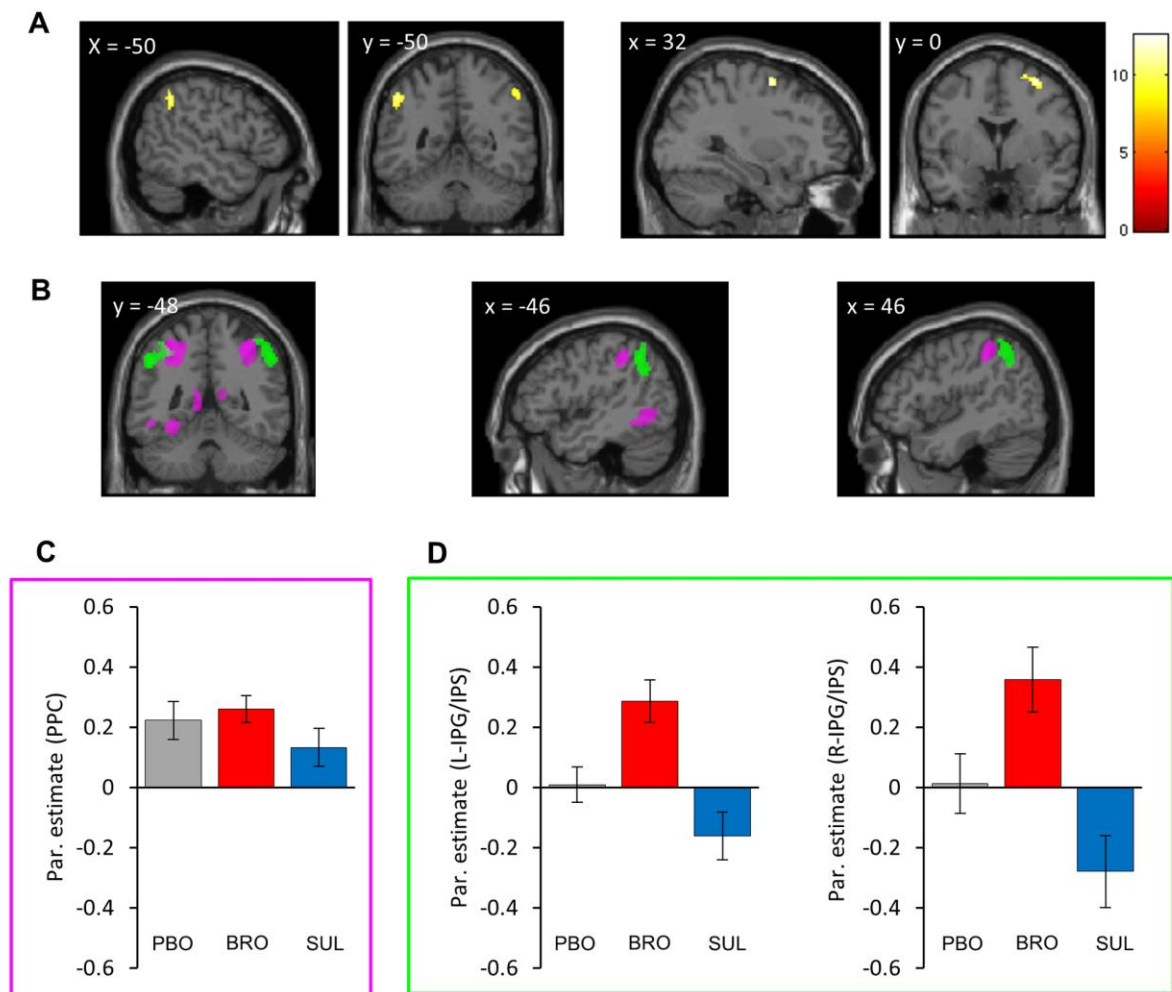
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Figure 3



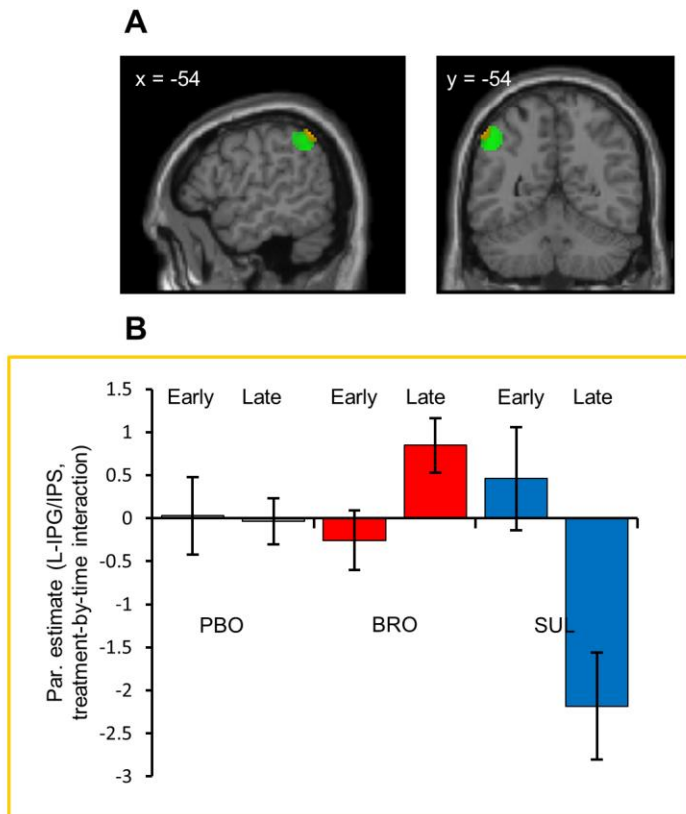
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Figure 4



Dopamine modulates the neural representation of subjective value of food in hungry subjects

Figure 5



Dopamine modulates the neural representation of subjective value of food in hungry subjects

Tables

Table 1 Regions correlated with subjective value.

Region	Side	Cluster Size	Peak MN coordinates			Peak scores	
			x	y	z	T	Z
Intraparietal Sulcus	L/R	7354	-26	-66	46	6.4	5.32
Middle Frontal Gyrus	L	425	-24	2	58	5.75	4.91
Middle Frontal Gyrus	R	744	25	-1	54	5.5	4.74
Fusiform Gyrus/Lingual Gyrus	R	833	28	-64	-8	5.24	4.57
Inferior Frontal Gyrus	R	604	50	6	26	4.86	4.3
Middle Frontal Gyrus	R	286	46	42	10	4.25	3.86
Inferior Frontal Gyrus	L	248	-48	2	34	4.1	3.74
Anterior Cingulate/Medial Frontal Gyrus*	L/R	81	0	44	2	3.71	3.43

p<0.05 whole-brain FWE correction for multiple comparisons at the cluster-level (p<0.001 uncorrected threshold).

*Survives p<0.05 small-volume FWE correction within a 10mm sphere around the vmPFC coordinates (-3, 42, -6) from the work of Chib et al. (2009).

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Table 2 Regions exhibiting a dopaminergic modulation of the neural representation of value.

Region	Side	Cluster Size	Peak MNI coordinates			Peak scores	
			x	Y	Z	F	Z
Middle Frontal Gyrus	R	55	32	0	58	12.62	3.86
Inferior Parietal Gyrus/Intraparietal Sulcus	L	63	-50	-50	46	11.17	3.63
Inferior Parietal Gyrus/Intraparietal Sulcus	R	40	52	-50	48	9.95	3.42

p<0.001 uncorrected, extent k>20 voxels.

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Table 3 Regions with an enhanced neural representation of value under bromocriptine, compared to sulpiride.

Region	Side	Cluster Size	Peak MNI coordinates			Peak scores	
			x	y	Z	T	Z
Inferior Parietal Gyrus/Intraparietal Sulcus	L	494	-50	-50	46	4.66	4.14
Inferior Parietal Gyrus/Intraparietal Sulcus	R	363	52	-50	48	4.45	3.99

p<0.05 whole-brain FWE correction for multiple comparisons at the cluster-level (p<0.001 uncorrected threshold).

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Table 4 Activation peak exhibiting a time-by-treatment interaction in the left IPG/IPS.

Region	Side	Cluster Size	Peak MNI coordinates			Peak scores	
			X	Y	Z	F	Z
Inferior Parietal Gyrus/Intraparietal Sulcus	L	10	-54	-54	50	8.79	3.39

p<0.05 small-volume FWE correction within a 10mm sphere around the peak voxel in the left IPG/IPS (-50,-50, 46) which showed an effect of drug across the entire bidding trial (model 1).