

Dopamine and intertemporal choice in humans

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Abstract: The dopamine (DA) system has been implicated in the mediation of cost/benefit evaluations involved in the intertemporal choices between immediate and delayed rewards. This involvement was further investigated in two studies of normal participants that had to decide between a smaller immediate and a larger delayed reward in a series of 27 decisions. In study 1 the dopamine D2/D3 receptor agonist pramipexole or placebo were administered in a double-blind cross-over protocol prior to the decisions. In study 2 the same experiment was conducted in two groups of normal participants that were homozygous for either the 7-repeat or the 4 repeat variant of the exon III polymorphism of the dopamine D4 receptor gene. Dopaminergic involvement is highlighted by the results.

Keywords: intertemporal choice; dopamine; impulsivity; dopamine D4 receptor; dopamine agonist

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Zusammenfassung: Das Dopamin (DA) System ist mit Kosten / Nutzen Abschätzungen zum Beispiel bei so genannten "Intertemporal Choice" Aufgaben in Verbindung gebracht worden. Hierbei handelt es sich um Aufgaben, bei denen zwischen einem (kleineren) sofort verfügbaren und einem später verfügbaren (größeren) Gewinn unterschieden werden muss. Es kommt zu einer Abwertung von später verfügbaren Gewinnen, wobei die Abwertungskurve einer hyperbolen Funktion folgt. Wir haben die Rolle des Dopamins in zwei weiteren Untersuchungen näher charakterisiert, die jeweils 27 Entscheidungen zwischen einem frühen und einem späteren Gewinn beinhalteten. Das Paradigma erlaubte die Schätzung der Steilheit der Abwertungskurve und teilte die Einzelentscheidungen darüber hinaus nach der Höhe des Gewinns in „niedrige“, „mittlere“ und „hohe“ Gewinne ein. In Studie 1 wurde die Abwertung unter Placebo mit dem Dopaminagonist Pramipexol verglichen (doppel-blindes Cross-Over Design). In der Placebobedingung wurde ein typischer Effekt der Belohnungsgröße mit weniger steiler Abwertung von großen Gewinnen gesehen. Dies war unter Pramipexol nicht der Fall, Probanden waren also weniger konservativ.

In Studie 2 untersuchten wir zwei Gruppen normaler Probanden die sich bezüglich der von ihnen getragenen Variante des Dopamin-D4-Rezeptors unterschieden (homozygot für die 7-Repeat oder 4-Repeat Variante des Exon III Polymorphismus). Träger der 7-Repeat Variante werteten Gewinner steiler ab als Träger der 4-Repeat-Variante. Erstere ist mit Impulsivität in Zusammenhang gebracht worden.

Keywords: intertemporal choice; Dopamin; Impulsivität; Dopamin D4 Rezeptor; Dopaminagonist

Introduction

One of the secrets for the success of the human species is the ability to withhold from the consumption of an immediately available reward in order to attain a larger but delayed reward. As an extreme, in human economic behaviour the return on financial investments is sometimes collected only after years or even decades (Rosati et al., 2007). In animals much shorter delays can be observed (Amiez et al., 2006; Kalenscher et al., 2005) but it has been assumed that analogous neural systems are active in ani-

mals and humans in weighting immediate smaller against delayed larger rewards.

In humans, McClure et al. (2004, 2007), on the basis of functional MRI data obtained in temporal discounting tasks involving either primary (juice) or monetary rewards and inspired by economic theories, proposed the existence of two different brain systems: a "β-system" comprising the ventral striatum, medial prefrontal cortex, and orbitofrontal cortex associated with choices involving immediate rewards, and a δ-system encompassing prefrontal and parietal regions which is thought to be active in all intertemporal choices, i. e.



not just those decisions involving an immediate reward. The β -areas *sensu McClure* have been found in multiple brain imaging studies involving reward processing (Delgado, 2000; Everitt & Robbins 2005; Riba et al., 2008) or reward expectation (Knutson et al., 2005). Importantly, the ventral striatum is an area that is richly innervated by dopaminergic (DA) neurons arising from the midbrain therefore putting this neuromodulatory system in a key position to govern intertemporal choice. In the current report, we seek further evidence for a role of the DA-system in intertemporal choice by two approaches in normal human participants: in a first study we use a pharmacological manipulation (acute administration of the dopamine D2/D3 receptor agonist pramipexole) following a double-blind placebo-controlled crossover design, whereas in the second study participants differing in a DA-related gene previously associated to novelty-seeking and impulsive behaviour were studied.

Pharmacological evidence for a role of DA in risky behaviour and intertemporal choice

In animals, it has been convincingly shown that blockade of DA receptors by neuroleptic agents shifts the animal's behaviour to preferring smaller immediate rewards and rewards that are more easy to obtain (Cardinal et al., 2000; Denk et al., 2005; Salamone et al., 2001; van Gaalen et al., 2006). Amphetamine, on the other hand, has yielded mixed effects in intertemporal choice tasks (Floresco et al., 2008). Interest in how DA may alter risk-based decision making has increased recently in light of clinical reports linking the use of DA receptor agonists to the development of pathological gambling in patients with Parkinson's disease and restless legs syndrome (Gallagher et al., 2007; Quickfall & Suchowersky 2007). This effect appears to be specific to DA receptor agonists, as pathological gambling has not been seen in patients on levodopa monotherapy (Gallagher et al., 2007). Interestingly, patients on dopamine agonist medication have previously been shown to show altered behaviour in gambling (Cools et al., 2003) and probabilistic learning (Frank et al., 2007) tasks. Thus, the role of the dopaminergic system in the modulation of risky choices is firmly established. To our knowledge no previous study has examined the influence of a dopaminergic agonist on intertemporal choice behaviour, however. In the present investigation following earlier work in our laboratory on a gambling task (Riba et al., 2008) we therefore tested the effect of a single dose of the D2/D3 receptor agonist pramipexole on intertemporal choice in normal healthy adults.

Interindividual genetic differences in the dopaminergic system

Another way to assess the contribution of dopaminergic functioning to intertemporal choice is to examine genetic differences in the normal population. Indeed, polymor-

phisms in several DA-related genes have been found to predict risky behaviour, novelty-seeking, or impulsive / addictive behaviour patterns. Studies have looked at genes coding the D2 receptor (Comings et al., 1996; De et al., 2001), D4 receptor (Benjamin et al., 1996; Li et al., 2006; Perez De Castro et al., 1997), D1 receptor (De et al., 1997), and the DA transporter (De et al., 2001). Specifically studying temporal discounting, Boettiger et al. (2007) not only demonstrated that the Val158Met polymorphism of the catechol-O-methyltransferase gene predicted impulsive choice behaviour but also found that it was predictive of activity levels in the dorsolateral prefrontal cortex and posterior parietal cortex during decision making.

In the present study we focussed on the D4 receptor that has been previously demonstrated to be related to pathological gambling (Perez De Castro et al., 1997) as well as to executive and action monitoring functions (Durstun et al., 2005; Fossella et al., 2002; Krämer et al., 2007; Okuyama et al., 1999; Strobel et al., 2004). The VNTR investigated in the present study is an extensive polymorphic 48bp sequence in exon III that is coding for the third intracellular loop in the D4 receptor (Lichter et al., 1993; Van Tol et al., 1992; Wong & Van Tol 2003). Importantly, the 7-repeat variant has not only been shown to be half as potent in its ability to inhibit cyclic adenosine monophosphate (cAMP) formation compared to the 2- or 4-repeat variants (Asghari et al., 1995), but also appears to be associated with attention deficit hyperactivity disorder (Faraone et al., 2001; Li et al., 2006; Maher et al., 2002) and possibly the personality trait novelty seeking (Paterson et al., 1999; Schinka et al., 2002). Interestingly, reduced inhibitory control in carriers of at least one 7-repeat allele compared to participants with other variants of the DRD4 genes has been found in healthy participants (Congdon et al., 2007).

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The present experiments

To further pinpoint the role of the dopaminergic system in intertemporal choice, we conducted two behavioural experiments. In the first, young healthy participants received a single dose of pramipexole (or placebo) prior to taking repeated choices between a smaller immediate and a larger delayed monetary reward. In the second, the same behavioural paradigm was administered to two groups of healthy individuals being homozygous for either the 7 repeat or the 4 repeat variant of the exon III VNTR of the DRD4. As empirical evidence in humans suggests that future gains are discounted in a hyperbolic or quasi-hyperbolic fashion (Frederick et al., 2003; Laibson 1997), we modelled the participants' behaviour according to the following formula (Mazur 1984):

$$V = \frac{A}{1 + kD}$$

where V is the present value of the delayed reward A after a delay D , and k is the *temporal discount rate*. By requiring our participants to make decisions on multiple trials differing in their delay, their ratio between the delayed and the immediate reward and the absolute size of the involved rewards, we were able to determine each participant's temporal discounting parameter k (following a method suggested by Kirby et al., 1999). Importantly, the design featured trials differing in magnitude of the large delayed reward which could range from small (25 and 35 Euro), to medium (50 and 60 Euro), to large (75 and 85 Euro). Prior studies have revealed a "magnitude effect" in that that larger rewards are typically discounted at lower rates (Benzion et al., 1989; Green et al., 1994; Green et al., 1994; Kirby 1997; Kirby and Marakovic 1995, 1996; Raineri and Rachlin 1993; Thaler 1981). We were thus in the position to investigate the effects of the experimental manipulation of the overall k and on the magnitude effect.

Material and methods

Study 1

Participants

Sixteen male volunteers (mean age 25 years, range 21 to 28 years) participated in this study. They were right-handed and had normal or corrected-to-normal vision. None of them had a history of neurological or psychiatric disorder. All of them gave written informed consent and were paid according to their performance in the task (see below).

Medication

The study was conducted according to a double-blind randomized crossover design. All volunteers received the two study medications, i.e., pramipexole and placebo, each participant thus acting as his own control. Volunteers participated in two different experimental sessions, separated at least by one week. On each experimental session participants received 20 mg domperidone in a non-blind fashion in order to antagonize any potential nausea induced by pramipexole. They also received either placebo (lactose) or 0.5 pramipexole hydrochloride (packaged in identical capsules) in a double blind fashion according to a randomization table. Half of the subjects received placebo in the first experimental session and pramipexole in the second. The other half received pramipexole in the first session and placebo in the second.

Task

A version of the monetary-choice task devised by Kirby et al. (1999) was used. On a sheet of paper, participants were given a fixed set of 27 choices between a smaller immediate reward (SIR) and larger delayed reward (LDR; see Table 1)

stated in Euro (1 Euro \approx 1.50 US\$ at the time of writing). The order of trials was fixed and arranged such that the trial order did neither correlate with the SIR or LDR amounts, nor with the temporal difference, delay or the discounting rate. Please note that the design featured trials of three different classes of magnitude: small (LDR between 25 and 35 Euro), medium (LDR between 50 and 60 Euro), and large (LDR between 75 and 85 Euro).

Participants were informed prior to the experiment that they would have the chance of receiving the outcome of *one* of their 27 decisions after the completion of the experiment.

Table 1. Choices given to the participants. SIR = small immediate reward, LDR = large delayed reward, K indiff = temporal discounting value at which the two decisions are of equal subjective value, K rank = trials were ranked according to K indiff into 9 classes, LDR size = the size of the delayed reward was classified as small (S, between 25 and 35 €), medium (M, between 50 and 60 €) and large (L, between 75 and 85 €). Please note that a fixed order was used such as to assure that k rank and LDR size and delay were not correlated with serial position.

| Order | SIR | LDR | Delay (days) | K indiff | K rank | LDR size |
|-------|------|------|--------------|----------|--------|----------|
| 13 | € 34 | € 35 | 186 | .00016 | 1 | S |
| 1 | € 54 | € 55 | 117 | .00016 | 1 | M |
| 9 | € 78 | € 80 | 162 | .00016 | 1 | L |
| 20 | € 28 | € 30 | 179 | .00040 | 2 | S |
| 6 | € 47 | € 50 | 160 | .00040 | 2 | M |
| 17 | € 80 | € 85 | 157 | .00040 | 2 | L |
| 26 | € 22 | € 25 | 136 | .0010 | 3 | S |
| 24 | € 54 | € 60 | 111 | .0010 | 3 | M |
| 12 | € 67 | € 75 | 119 | .0010 | 3 | L |
| 22 | € 25 | € 30 | 80 | .0025 | 4 | S |
| 16 | € 49 | € 60 | 89 | .0025 | 4 | M |
| 15 | € 69 | € 85 | 91 | .0025 | 4 | L |
| 3 | € 19 | € 25 | 53 | .0060 | 5 | S |
| 10 | € 40 | € 55 | 62 | .0060 | 5 | M |
| 2 | € 55 | € 75 | 61 | .0060 | 5 | L |
| 18 | € 24 | € 35 | 29 | .016 | 6 | S |
| 21 | € 34 | € 50 | 30 | .016 | 6 | M |
| 25 | € 54 | € 80 | 30 | .016 | 6 | L |
| 5 | € 14 | € 25 | 19 | .041 | 7 | S |
| 14 | € 27 | € 50 | 21 | .041 | 7 | M |
| 23 | € 41 | € 75 | 20 | .041 | 7 | L |
| 7 | € 15 | € 35 | 13 | .10 | 8 | S |
| 8 | € 25 | € 60 | 14 | .10 | 8 | M |
| 19 | € 33 | € 80 | 14 | .10 | 8 | L |
| 11 | € 11 | € 30 | 7 | .25 | 9 | S |
| 27 | € 20 | € 55 | 7 | .25 | 9 | M |
| 4 | € 31 | € 85 | 7 | .25 | 9 | L |

Wins were determined in a two step procedure. First, participants were to throw a dice. In case of a “six” they were allowed to draw a trial number (1 to 27, written on small sheets of folded paper). The participant’s decision (immediate or delayed choice) was derived from the paper-record. If the participant had chosen the immediate reward, he received the sum in cash, in case of a choice for the delayed reward the sum was transferred to the participant’s bank account after the appropriate delay period. Of the 16 participants 3 received a reward.

Behavioural Analysis

The computation of the individual discounting rate parameter (k-rate) was performed as described by Kirby et al. (1999). In brief, a participant with a k-rate coinciding with the k of certain choice would be indifferent to this selection. For example, if he had a k-rate of 0.001, he would be indifferent to the selection 67 € now or 75 € in 119 days (see Table 1). If he had a greater individual k-rate, he would select the immediate reward. Then, choices with the next k-value were examined (i.e., 49 € now or 60 € in 89 days, corresponding to $k = 0.0025$). If the participant selected the delayed reward in this case, the individual k-rate was calculated to be the geometric mean of the two k-values, that is 0.0016. As not all the decisions of a participant were perfectly consistent, the individual k-rate was specified to yield the highest proportion of choices consistent with that value. We also computed the consistency of the k-rate (percentage of participant’s choices that were consistent with their assigned discount rate). Treatment effects on k-values obtained for the entire range of 27 decisions and consistency were compared by paired t-test.

As the trials could be grouped into small medium and large rewards (see table 1), separate k-values for the three different reward magnitudes were obtained and entered into an ANOVA design with treatment (placebo, pramipexole) and magnitude (small, medium, large) as factors. Prior to all statistical tests k-values were log-transformed to allow parametric testing.

Study 2

Participants and Genotyping

Genotyping was performed in a large sample of 656 students from the University of Barcelona (491 women; age range from 18 to 56, mean = 21.7, S.D. = 3.5), who underwent a comprehensive neuropsychological test battery and filled out several personality questionnaires. We initially performed the genotyping for six different polymorphisms in the dopaminergic system, namely COMT Val108/158Met, DRD4 -521, DRD4 120bp, DRD4 exon III, MAO-A 30bp and DAT1 VNTR. In the present study

we focused on the DRD4 exon III polymorphism only. The allele frequencies for this polymorphism were as follows: 8.7% (2-repeat), 2.7% (3-repeat), 70.9% (4-repeat), 1.5% (5-repeat), 0.3% (6-repeat) and 15.9% (7-repeat). 29 participants were homozygous for the 7-repeat allele.

We contacted homozygous 7-repeat and 4-repeat participants of the large genotyped sample and 25 volunteered to take part in the current experiment (20 women; age range from 18 to 28 years, mean = 21.2). Of these participants, 10 (8 women) were homozygous for the 7-repeat version (in the following referred to as 7rep group) and 15 (12 women) were carriers of two 4-repeat alleles (in the following referred to as 4rep group). All participants were right-handed participants of European ancestry (except one from Ecuador) and were free of neurological and psychiatric disorders (self-report). They were paid for their participation and gave written informed consent.

DNA contributed to the study was prepared by standard techniques from two independent EDTA blood samples of each participant. DNA was amplified with fluorescent primers: DRD4_ExIII_for: 5'-Fam-GCGACTACGTGGTC-TACTCG-3', DRD4_ExIII_rev: 5'-AGGACCCTCATGG-CCTTG-3'. 2mM MgCl₂ and 10% Q-Solution were added to the reaction mix. Due to reduced amplification of the 7-repeat allele in comparison to shorter repeat alleles, the elongation time was increased. The following cycling conditions were used: 95 °C 15', (98 °C 15', 62 °C 30'', 72 °C 1') x 34 cycles, 72 °C 10'. To determine fragment length PCR products were analyzed on an ABI 3100 automated sequencer with a fluorescence detection system.

Genotypes of participants selected for the current study were controlled in an independent second DNA sample by direct sequencing using the ABI PRISM BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, USA). Sequencing products were resolved on an ABI 3100 automated sequencer (Applied Biosystems, Foster) and analyzed using the Staden Package (Bonfield et al., 1995a,b).

Behavioural Analysis

The behavioural analysis was conducted analogously to study 1. Because a between groups design was used here, the appropriate between-groups statistical procedures were chosen.

Results

Study 1

The mean temporal discount rates are illustrated in figure 1. Even though discount rates were numerically slightly higher under pramipexole, this difference was not signifi-

cant ($t(15) = 1.06$, n.s.). The consistency (percentage of participant's choices that were consistent with their assigned discount rate) was $95.3 \pm 3.1\%$ under placebo and $94.2 \pm 5.5\%$ under pramipexole and thus did not differ between conditions ($t(15) = 1.09$, n.s.).

When trials with small, medium, and large delayed rewards were considered separately (figure 2), it became apparent that the two treatments led to different discounting rates for the different reward sizes. Whereas for placebo the typical smaller discount rate was seen for larger rewards compared to smaller rewards, this was not the case for pramipexole. An ANOVA with treatment and reward size revealed a main effect of reward size ($F(2,30) = 8.41$, $p < 0.0015$) as well as an interaction of treatment and reward size ($F(2,30) = 3.6$, $p = 0.04$). This was due to a significant difference of discounting rates for large rewards ($t(15) = 2.33$, $p < 0.04$).

Study 2

The mean temporal discount rates are illustrated in figure 3 and were highly similar for both genetic groups ($t(23) = 0.26$, n.s.). Participants homozygous for the 7rep allele were significantly less consistent in their choices ($91.4 \pm 3.5\%$) than the 4rep homozygous volunteers ($94.6 \pm 3.0\%$; $t(23) = 2.32$, $p = 0.029$).

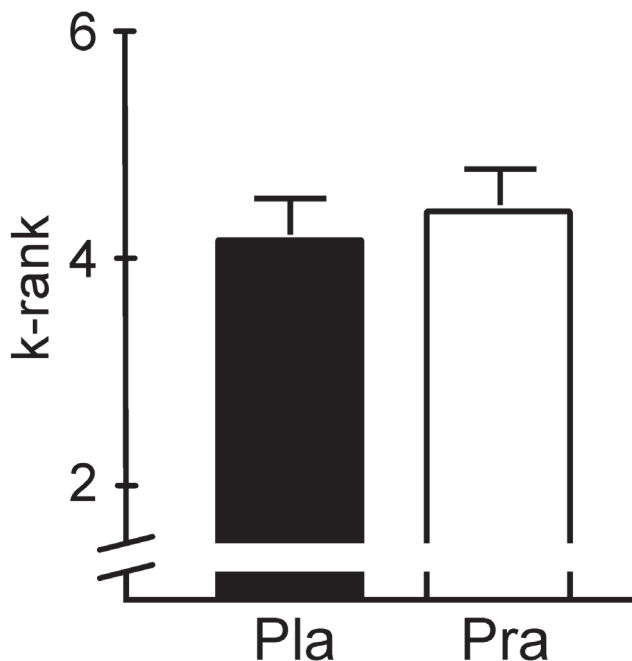


Figure 1. Study 1, pramipexole vs. placebo. Overall discounting rate (expressed in terms of k-rank, see table 1). There is no difference between the two conditions if all decisions are used to estimate individual k. Pla: placebo, Pra: pramipexole.

When trials were grouped into those with small, medium and large delayed rewards (figure 4), a different pattern emerged for the two groups: the 7 rep participants showed a higher k-value than the 4 rep homozygous group for small rewards, whereas for large rewards their k-values were smaller. An ANOVA yielded a highly significant effect of reward magnitude ($F(2,46) = 17.8$, $p < 0.0001$) and a marginally significant group \times magnitude effect ($F(2,46) = 2.84$, $P = 0.0686$). When only small and large rewards were considered, the group \times magnitude interaction became significant ($F(1,23) = 4.85$, $p < 0.04$; main effect magnitude: $F(1,23) = 30.68$, $p < 0.0001$; main effect group $F(1,23) = 0.02$, n.s.).

Discussion

In the introduction we outlined a number of arguments for a role of the dopaminergic system in temporal discounting. The present study therefore examined the effects of a dopaminergic agonist (study 1) and of a polymorphism of the dopamine D4 receptor (study 2) on temporal discounting behaviour. Interestingly, neither of the two studies revealed an effect on the overall discounting rate k.

However, when the magnitude of the late reward was considered, both studies showed differential modulation of the magnitude effect. Previous studies using both, real rewards (Kirby 1997; Kirby & Marakovic 1995, 1996) and hypothetical rewards (Benzion et al., 1989; Green et al., 1994; Green et al., 1994; Raineri & Rachlin 1993; Thaler

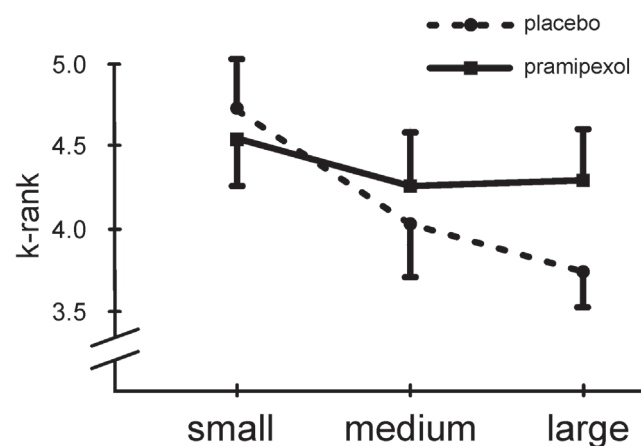


Figure 2. Study 1, pramipexole vs. placebo. Discounting rate (expressed in terms of k-rank, see table 1) separately for trials with small, medium and large delayed rewards. A clear difference emerged in the magnitude effect on k: Whereas the typical pattern with less steep discounting is seen under placebo, this is not the case under pramipexole. See text for statistical results.

1981) have shown a magnitude effect on discount rates. This effect specifically refers to the finding that larger rewards are typically discounted at lower rates.

Before we discuss the differential modulations of the magnitude effect in studies 1 and 2 in more detail, it is important to remind oneself that as k increases a person discounts the future more steeply. A larger k indicates a longer duration of the so-called window of vulnerability, i.e. the period of time during which a person will opt for the smaller, ear-

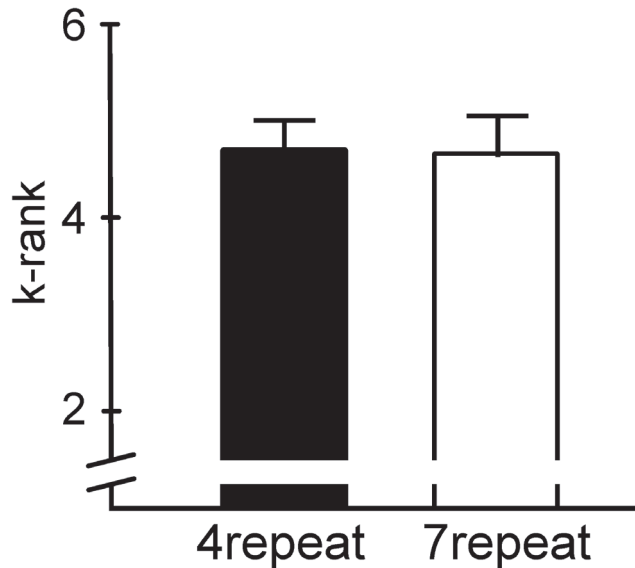


Figure 3. Study 2, DRD4 exon III polymorphism. Overall discounting rate (expressed in terms of k -rank, see table 1). There is no difference between the participants homozygous for the 7repeat and 4repeat variant of the polymorphism if all decisions are used to estimate individual k .

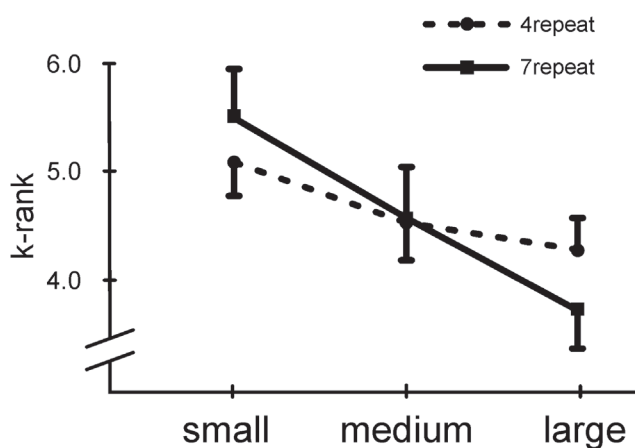


Figure 4. Study 2, DRD4 exon III polymorphism. Discounting rate (expressed in terms of k -rank, see table 1) separately for trials with small, medium and large delayed rewards. A clear difference emerged in the magnitude effect on k : 7repeat participants discounted smaller delayed rewards more steeply than 4repeat participants. See text for statistical results.

lier reward. It has therefore been suggested that k can be viewed as an impulsiveness parameter, with higher k corresponding to greater degrees of impulsiveness.

Study 1: Dopamine agonist effect

In the placebo condition the typical magnitude effect was observed, i.e. the k -value was considerably smaller for larger than for smaller delayed rewards. This is consistent with a host of earlier studies (Benzion et al., 1989; Green et al., 1994; Kirby 1997; Kirby & Marakovic 1995, 1996; Raineri & Rachlin 1993; Thaler 1981). By contrast, no magnitude effect was observed in the pramipexole condition. Specifically, larger delayed reward were associated with a significantly larger k -value compared to the placebo condition. Whereas people normally become less impulsive and more conservative in their decision behaviour when larger rewards are involved, this was not the case under pramipexole.

In other words, pramipexole led to more impulsive decisions when larger sums were at stake, i.e. precisely in situations that normally require the controlling actions of the d-system (McClure et al., 2004). Interestingly, in a recent fMRI study addressing the actions of pramipexole on reward expectation processes, we found that the ventral striatum's connectivity to medial prefrontal regions, i.e. regions forming part of the d-system, was greatly diminished under pramipexole compared to placebo (Ye et al., 2009). This pattern was interpreted as evidence for a weakened control of the ventral striatum by medial prefrontal cortex. Such a weakened control could also explain the lack of a magnitude effect in the pramipexole group in the current study.

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Study 2: DRD4 polymorphism

The DRD4 exon III polymorphism studied in the present experiment has been previously associated with impulsive behaviour and (Faraone et al., 2001; Li et al., 2006; Maher et al., 2002). In particular, the 7repeat allele has been implicated as being a risk factor for this condition. Moreover, reduced inhibitory control has been found in healthy carriers of at least one 7 repeat allele (Congdon et al., 2007). In the present investigation we found that participants homozygous for the 4repeat or 7repeat alleles showed a differential modulation of the magnitude effect. The 7repeat participants showed a considerably higher k -value for trials involving smaller delayed rewards but a smaller k -value for trials involving large rewards. This suggests that control of impulsivity kicking in for larger delayed rewards was unimpaired in homozygous carriers of the 7repeat allele. However, when smaller sums were promised as a delayed reward, these subjects discounted the value of such sums at a steeper rate than 4repeat participants. It is noteworthy that the 7repeat participants also were slightly less

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consistent in their choices than the 4repeat subjects. With regard to the dichotomy between the β - and d-systems, the pattern suggests that with large delayed rewards the 7repeat participants manage to engage the d-system in order to withhold from impulsive behavior, whereas they are not able to keep an overactive β -system at bay when smaller rewards are at stake.

Conclusions

Taken together the findings of both studies show that, in addition to the overall k-value, the size and form of the magnitude effect reveal important information about the discounting of future rewards. Moreover, we demonstrated that manipulations involving the dopaminergic system can have different effects on discounting behaviour. Whereas pramipexole abolished the magnitude effect and led to higher discount rates for decisions involving larger delayed rewards, the 7repeat allele of the D4 receptor led to higher discounting rates for small delayed rewards. The former effect seems to be compatible with a compromised action of the d-system which is required in particular for decisions involving higher stakes, while the latter pattern suggests that the D4 receptor effect resides in the β -system. Further studies using neuroimaging (Kable & Glimcher 2007; McClure et al., 2004, 2007) methodology are needed to substantiate the putative loci of the pramipexole and DRD4 effects on temporal discounting.

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References

- Amiez, C., Joseph, J.P. & Procyk, E. (2006) Reward encoding in the monkey anterior cingulate cortex. *Cerebral Cortex*, *16*, 1040–1055.
- Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V. & Van Tol, H.H. (1995). Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *Journal of Neurochemistry*, *65*, 1147–1165.
- Benjamin, J., Li, L., Patterson, C., Greenberg, B.D., Murphy, D.L. & Hamer, D.H. (1996). Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature Genetics*, *12*, 81–84.
- Benzion, U., Rapoport, A. & Yagil, J. (1989). Discount rates inferred from decisions: An experimental study. *Management Science*, *35*, 270–284.
- Boettiger, C.A., Mitchell, J.M., Tavares, V.C., Robertson, M., Joslyn, G., D'Esposito, M. & Fields, H.L. (2007). Immediate reward bias in humans: fronto-parietal networks and a role for the catechol-O-methyltransferase 158(Val/Val) genotype. *Journal of Neuroscience*, *27*, 14383–14391.
- Bonfield, J.K., Smith, K. & Staden, R. (1995). A new DNA sequence assembly program. *Nucleic Acids Research*, *23*, 4992–4999.
- Cardinal, R.N., Robbins, T.W. & Everitt, B.J. (2000). The effects of d-amphetamine, chlordiazepoxide, \pm -flupenthixol and behavioural manipulations on choice of signalled and unsignalled delayed reinforcement in rats. *Psychopharmacology*, *152*, 362–375.
- Comings, D.E., Rosenthal, R.J., Lesieur, H.R., Rugle, L.J., Muhleman, D., Chiu, C., Dietz, G. & Gade, R. (1996). A study of the dopamine D2 receptor gene in pathological gambling. *Pharmacogenetics*, *6*, 223–234.
- Congdon, E., Lesch, K.P. & Canli, T. (2008). Analysis of DRD4 and DAT polymorphisms and behavioral inhibition in healthy adults: implications for impulsivity. *American Journal of Medical Genetics B Neuropsychiatric Genetics*, *147B*, 27–32.
- Cools, R., Barker, R.A., Sahakian, B.J. & Robbins, T.W. (2003). L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia*, *41*, 1431–1441.
- De, C., Gade, R., Wu, S., Chiu, C., Dietz, G., Muhleman, D., Saucier, G., Ferry, L., Rosenthal, R.J., Lesieur, H.R., Rugle, L.J. & MacMurray, P. (1997). Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. *Molecular Psychiatry*, *2*, 44–56.
- De, C., Gade-Andavolu, R., Gonzalez, N., Wu, S., Muhleman, D., Chen, C., Koh, P., Farwell, K., Blake, H., Dietz, G., MacMurray, J.P., Lesieur, H.R., Rugle, L.J. & Rosenthal, R.J. (2001). The additive effect of neurotransmitter genes in pathological gambling. *Clinical Genetics*, *60*, 107–116.
- Delgado, M.R., Nystrom, L.E., Fissell, C., Noll, D.C. & Fiez, J.A. (2000). Tracking the hemodynamic responses to reward and punishment in the striatum. *Journal of Neurophysiology*, *84*, 3072–3077.
- Denk, F., Walton, M.E., Jennings, K.A., Sharp, T., Rushworth, M.F.S., Bannerman, D.M. (2005) Differential involvement of serotonin and dopamine systems in cost-benefit decisions about delay or effort. *Psychopharmacology*, *179*, 587–596.
- Durston, S., Fossella, J.A., Casey, B.J., Hulshoff Pol, H.E., Galvan, A., Schnack, H.G., Steenhuis, M.P., Minderaa, R.B., Buitelaar, J.K., Kahn, R.S. & van Engeland, H. (2005) Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. *Molecular Psychiatry*, *10*, 678–685.
- Everitt, B.J. & Robbins, T.W. (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature Neuroscience*, *8*, 1481–1489.
- Faraone, S.V., Doyle, A.E., Mick, E. & Biederman, J. (2001). Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *158*, 1052–1057.
- Floresco, S.B., Tse, M.T. & Ghods-Sharifi, S. (2008). Dopaminergic and glutamatergic regulation of effort- and delay-based decision making. *Neuropsychopharmacology*, *33*, 1966–1979.
- Fossella, J., Sommer, T., Fan, J., Wu, Y., Swanson, J.M., Pfaff, D.W. & Posner, M.I. (2002). Assessing the molecular genetics of attention networks. *BMC Neuroscience*, *3*, 14

- Frank, M.J., Samanta, J., Moustafa, A.A. & Sherman, S.J. (2007). Hold your horses: Impulsivity, deep brain stimulation, and medication in Parkinsonism. *Science*, *318*, 1309–1312
- Frederick, S., Loewenstein, G., & O'Donoghue, T. (2003). Time discounting and time preference: A critical review. In: Loewenstein, G., Read, D. & Baumeister, R. (eds.) Sage, New York, NY, pp 13–86.
- Gallagher, D.A., O'Sullivan, S.S., Evans, A.H., Lees, A.J. & Schrag, A. (2007). Pathological gambling in Parkinson's disease: Risk factors and differences from dopamine dysregulation. An analysis of published case series. *Movement Disorders*, *22*, 1757–1763.
- Green, L., Fristoe, N. & Myerson, J. (1994). Temporal discounting and preference reversals in choice between delayed outcomes. *Psychonomic Bulletin and Review*, *1*, 383–389.
- Green, L., Fry, A.F. & Myerson, J. (1994). Discounting of Delayed Rewards: A Life-Span Comparison. *Psychological Science*, *5*, 33–36.
- Kable, J.W. & Glimcher, P.W. (2007). The neural correlates of subjective value during intertemporal choice. *Nature Neuroscience*, *10*, 1625–1633.
- Kalenscher, T., Windmann, S., Diekamp, B., Rose, J., Gunturkun, O. & Colombo, M. (2005). Single units in the pigeon brain integrate reward amount and time-to-reward in an impulsive choice task. *Current Biology*, *15*, 594–602.
- Kirby, K.N. (1997). Bidding on the future: Evidence against normative discounting of delayed rewards. *Journal of Experimental Psychology-General*, *126*, 54–70.
- Kirby, K.N. & Marakovic, N.N. (1995). Modeling Myopic Decisions: Evidence for Hyperbolic Delay-Discounting within Subjects and Amounts. *Organizational Behavior and Human Decision Processes*, *64*, 22–30.
- Kirby, K.N. & Marakovic, N.N. (1996). Delay-discounting probabilistic rewards: Rates decrease as amounts increase. *Psychonomic Bulletin & Review*, *3*, 100–104.
- Kirby, K.N., Petry, N.M. & Bickel, W.K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *Journal of Experimental Psychology-General*, *128*, 78–87.
- Knutson, B., Taylor, J., Kaufman, M., Peterson, R. & Glover, G. (2005). Distributed neural representation of expected value. *Journal of Neuroscience*, *25*, 4806–4812.
- Krämer, U.M., Cunillera, T., Camara, E., Marco-Pallares, J., Cucurell, D., Nager, W., Bauer, P., Schule, R., Schols, L., Rodriguez-Fornells, A. & Münte, T.F. (2007). The impact of catechol-O-methyltransferase and dopamine D4 receptor genotypes on neurophysiological markers of performance monitoring. *Journal of Neuroscience*, *27*, 14190–14198.
- Laibson, D.i. (1997). Golden eggs and hyperbolic discounting. *Quarterly Journal of Economics*, *112*, 443–477.
- Li, D., Sham, P.C., Owen, M.J. & He, L. (2006). Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Human Molecular Genetics*, *15*, 2276–2284.
- Lichter, J.B., Barr, C.L., Kennedy, J.L., Van Tol, H.H., Kidd, K.K. & Livak, K.J. (1993). A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. *Human Molecular Genetics*, *2*, 767–773.
- Maher, B.S., Marazita, M.L., Ferrell, R.E. & Vanyukov, M.M. (2002). Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. *Psychiatric Genetics*, *12*, 207–215.
- Mazur, J.E. (1984). Tests of an equivalence rule for fixed and variable reinforcer delays. *Journal of Experimental Psychology Animal Behavior Processes*, *10*, 426–436.
- McClure, S.M., Ericson, K.M., Laibson, D.i., Loewenstein, G. & Cohen, J.D. (2007). Time discounting for primary rewards. *Journal of Neuroscience*, *27*, 5796–5804.
- McClure, S.M., Laibson, D.i., Loewenstein, G. & Cohen, J.D. (2004). Separate neural systems value immediate and delayed monetary rewards. *Science*, *306*, 503–507.
- Okuyama, Y., Ishiguro, H., Toru, M. & Arinami, T. (1999). A genetic polymorphism in the promoter region of DRD4 associated with expression and schizophrenia. *Biochemistry and Biophysical Research Communications*, *258*, 292–295.
- Paterson, A.D., Sunohara, G.A. & Kennedy, J.L. (1999). Dopamine D4 receptor gene: novelty or nonsense? *Neuropsychopharmacology*, *21*, 3–16.
- Perez De Castro, I., Ibanez, A., Torres, P., Saiz-Ruiz, J. & Fernandez-Piqueras, J. (1997). Genetic association study between pathological gambling and a functional DNA polymorphism at the D4 receptor gene. *Pharmacogenetics*, *7*, 345–348.
- Quickfall, J. & Suchowersky, O. (2007). Pathological gambling associated with dopamine agonist use in restless legs syndrome. *Parkinsonism and Related Disorders*, *13*, 535–536.
- Raineri, A. & Rachlin, H. (1993). The effect of temporal constraints on the value of money and other commodities. *Journal of Behavioral Decision Making*, *6*, 77–94.
- Riba, J., Kramer, U.M., Heldmann, M., Richter, S. & Münte, T.F. (2008). Dopamine agonist increases risk taking but blunts reward-related brain activity. *PLoS ONE*, *3*, e2479.
- Rosati, A.G., Stevens, J.R., Hare, B. & Hauser, M.D. (2007). The Evolutionary Origins of Human Patience: Temporal Preferences in Chimpanzees, Bonobos, and Human Adults. *Current Biology*, *17*, 1663–1668.
- Salamone, J.D., Wisniecki, A., Carlson, B.B. & Correa, M. (2001). Nucleus accumbens dopamine depletions make animals highly sensitive to high fixed ratio requirements but do not impair primary food reinforcement. *Neuroscience*, *105*, 863–870.
- Schinka, J.A., Letsch, E.A. & Crawford, F.C. (2002). DRD4 and novelty seeking: Results of meta-analyses. *American Journal of Medical Genetics*, *114*, 643–648.
- Strobel, A., Debener, S., Anacker, K., Müller, J., Lesch, K.P. & Brocke, B. (2004). Dopamine D4 receptor exon III genotype influence on the auditory evoked novelty P3. *Neuroreport*, *15*, 2411–2415.
- Thaler, R. (1981). Some empirical evidence on dynamic inconsistency. *Economics Letters*, *8*, 201–207.
- van Gaalen, M.M., van Koten, R., Schoffelmeer, A.N.M. & Vanderschuren, L.J.M.J. (2006). Critical Involvement of Dopaminergic Neurotransmission in Impulsive Decision Making. *Biological Psychiatry*, *60*, 66–73.
- Van Tol, H.H., Wu, C.M., Guan, H.C., Ohara, K., Bunzow, J.R., Civelli, O., Kennedy, J., Seeman, P., Niznik, H.B. & Jovanovic, V. (1992). Multiple dopamine D4 receptor variants in the human population. *Nature*, *358*, 149–152.
- Wong, A.H. & Van Tol, H.H. (2003). The dopamine D4 receptors and mechanisms of antipsychotic atypicality. *Progress in Neuropsychopharmacology and Biological Psychiatry*, *27*, 1091–1099.
- Ye, Z., Hammer, A., Camara, E. & Münte, T.F. (2011). Pramipexole modulates the neural network of reward anticipation. *Human Brain Mapping*, *32*, 800–811.
- Zaki, J., Weber, J., Bolger, N. & Ochsner, K. (2009). The neural bases of empathic accuracy. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 11382–11387. ((Nicht in Text))
- Zysset, S., Huber, O., Ferstl, E. & von Cramon, D.Y. (2002). The anterior frontomedian cortex and evaluative judgment: An fMRI study. *NeuroImage*, *15*, 983–991.

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