BRAIN RESEARCH 1473 (2012) 63–77

Available online at www.sciencedirect.com

SciVerse ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

A functional neuroimaging study assessing gender differences in the neural mechanisms underlying the ability to resist impulsive desires

Esther K. Diekhof[a,b,*], Maria Keil[a], Katrin U. Obst[a,c], Ilona Henseler[a,d], Peter Dechent[e], Peter Falkai[a], Oliver Gruber[a]

[a]Center for Translational Research in Systems Neuroscience and Psychiatry, Department of Psychiatry, Georg August University, Goettingen, Germany

[b]University of Hamburg, Biocenter Grindel and Zoological Museum, Institute for Human Biology, Martin-Luther-King Platz 3, D-20146, Hamburg, Germany

[c]Friedrich Schiller University Jena, Institute of Psychology, Department of Social Psychology, Jena, Germany

[d]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

[e]University Medical Center Goettingen, MR-Research in Neurology and Psychiatry, Georg August University, Goettingen, Germany

ARTICLE INFO

Article history:
Accepted 7 July 2012
Available online 16 July 2012

Keywords:
fMRI
Psychophysiological interaction
Impulsivity
Frontopolar cortex
Ventral striatum

ABSTRACT

There is ample evidence of gender differences in neural processes and behavior. Differences in reward-related behaviors have been linked to either temporary or permanent organizational influences of gonadal hormones on the mesolimbic dopamine system and reward-related activation. Still, little is known about the association between biological gender and the neural underpinnings of the ability to resist reward-related impulses. Here we assessed with functional magnetic resonance imaging which neural processes enable men and women to successfully control their desire for immediate reward when this is required by a higher-order goal (i.e., during a 'desire-reason dilemma'; Diekhof and Gruber, 2010). Thirty-two participants (16 females) were closely matched for age, personality characteristics (e.g., novelty seeking) and behavioral performance in the 'desire-reason task'. On the neural level, men and women showed similarities in the general response of the nucleus accumbens and of the ventral tegmental area to predictors of immediate reward, but they differed in additional brain mechanisms that enabled self-controlled decisions against the preference for immediate reward. Firstly, men exhibited a stronger reduction of activation in the ventral pallidum, putamen, temporal pole and pregenual anterior cingulate cortex during the 'desire-reason dilemma'. Secondly, connectivity analyses revealed a significant change in the direction of the connectivity between anteroventral prefrontal cortex and nucleus accumbens during decisions counteracting the reward-related impulse when comparing men and women. Together, these findings support the view of a sexual dimorphism that manifested in the recruitment of gender-specific neural resources during the successful deployment of self-control.

*Corresponding author at: University of Hamburg, Institute for Human Biology, Biocenter Grindel and Zoological Museum, Martin-Luther-King Platz 3, D-20146 Hamburg, Germany. Fax: +49 40 42838 3937.
E-mail address: esther.diekhof@uni-hamburg.de (E.K. Diekhof).

0006-8993/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.brainres.2012.07.010

1. Introduction

Biological sex has a significant impact on mammalian brain structure and function (Arnold, 2004; Cahill, 2006). Sex chromosomes, sex-specific gene expression and prenatal levels of gonadal hormones that interact with sex steroid receptors in various brain regions may originally shape sexually dimorphic brain circuitries and thus constitute the basis for organizational gender differences. The significant increase in levels of gonadal hormones starting with the onset of puberty may then further add to these organizational differences, promoting obvious gender dimorphisms in adult brain physiology, in several cognitive functions and in the prevalence of various psychiatric disorders (Goldstein et al., 2001; Qureshi and Mehler, 2010; Paus, 2010; Hines, 2011).

Since the advent and the rise of in vivo neuroimaging methods like magnetic resonance imaging (MRI) several structural and functional gender differences have been reported in the human reward system in particular. On the structural level, it has been shown that the volume of lateral orbital and dorsomedial prefrontal subregions (including parts of the cingulate cortex) may be significantly higher in female than in male subjects relative to overall cerebrum size (Goldstein et al., 2001). In contrast, the volumes of ventromedial prefrontal subregions like the gyrus rectus, and subcortical brain regions like the globus pallidus and the putamen were found to be significantly enhanced in men compared to these structures in women (Goldstein et al., 2001; Rijpkema et al., 2012). In parallel, functional neuroimaging studies demonstrated that men exhibited more reward-related activation in the ventral striatum (e.g., the putamen) and orbitofrontal cortex (OFC) than women during successful performance of a computer game (Hoeft et al., 2008). In addition, male subjects also showed a significant increase in activation of the ventral striatum during anticipation of an uncertain reward, while women showed a stronger response of the anteroventral prefrontal cortex (avPFC) during reward delivery (Dreher et al., 2007). These gender differences in human brain physiology and reward-related behaviors may in part be a result of inter-individual differences in the concentrations of (cycling) gonadal steroids (Dreher et al., 2007; Rupp et al., 2009; Alonso-Alonso et al., 2011; see also Butera (2010)). In fact, direct evidence from rodent studies already suggests that high levels of estrogens (especially of 17β-estradiol) in the female brain may increase dopaminergic transmission and release in the ventral striatum (in particular in the nucleus accumbens (Nacc)), which may be accomplished through both direct and indirect manipulation of dopamine receptors and inhibitory synapses (e.g., Becker, 1999; Febo et al., 2005). Similarly, in male rodents the steroid hormone testosterone has been shown to impact on the Nacc, supposedly through its metabolites dihydrotestosterone and 3α-androstanediol, promoting behavioral effects that mimic those of rewarding drugs (e.g., Frye et al., 2002; DiMeo and Wood, 2006).

Nevertheless, despite a beginning understanding of the neurophysiological basis of gender differences in reward processing, the current neuroimaging evidence is far from being exhaustive. In particular, the field of human decision making and self-control (i.e., the ability to control reward-related behavioral impulses) has been widely ignored so far. The present study was therefore intended to further elucidate the association between 'gender' and human brain function during performance of an established self-control task (Diekhof and Gruber, 2010; Diekhof et al., in press). In particular, we were interested in gender differences in the neural underpinnings of the ability to successfully work for a higher-order long-term goal, when being confronted with an immediate, but suboptimal reward option. We thereby wanted to examine changes in regional brain activation in the situation, in which subjects were not allowed to collect predictors of an immediate reward during pursuit of the superordinate long-term goal. This situation is called 'desire-reason dilemma' (see Diekhof and Gruber, 2010; Diekhof et al., in press) (Fig. 1). Based on our previous observations we expected to find a significant down-regulation of reward-related activation in the nucleus accumbens and the dopaminergic midbrain during successful resolution of a 'desire-reason dilemma'. Furthermore, the downregulation of the right Nacc should be accompanied by an increased negative coupling with the left avPFC (i.e., the term 'avPFC' refers to the ventral part of the frontomarginal sulcus; see also Diekhof and Gruber, 2010), which may be necessary to successfully counteract the desire for immediate reward (Diekhof and Gruber, 2010; Diekhof et al., in press; see also Abler et al., 2012).

Apart from that, we further predicted that the dilemma-related reduction in mesolimbic activation as well as the degree and direction of the prefrontostriatal connectivity would be modulated by participants' "gender". This assumption was based on two lines of evidence: firstly, it has been demonstrated that the dopaminergic response of the ventral striatum (and associated structures) to predictors of reward and to pharmacological challenge with glucose or d-amphetamine may be enhanced in men compared to women (Haltia et al., 2007, 2008; Munro et al., 2006). In contrast, during the resting state an increased presynaptic dopamine synthesis capacity and striatal dopamine concentration has been found in women (Laakso et al., 2002; Pohjalainen et al., 1998), although less consistently across studies (see Best et al., 2005; Burke et al., 2011; Farde et al., 1995; van Dyck et al., 1995, who observed no gender dimorphism in the striatal dopaminergic response at rest). Secondly, in men the hemodynamic response of the ventral striatum and associated structures was significantly enhanced during expectancy of a salient reward (Dreher et al., 2007) and during behavioral success in a taxing behavioral task (Hoeft et al., 2008). It thus appears as if regions of the mesolimbic dopamine system of men are more responsive to predictors of reward as well as to salient outcomes. In the context of the present self-control task one would therefore assume that this gender dimorphism in the responsiveness of mesolimbic regions may modulate brain activation related to the conditioned (rewarding) stimuli. In particular, in the male sample a heightened responsiveness to predictors of immediate reward should specifically interfere with the ability to control reward-related impulses during the 'desire-reason dilemma'. We therefore predicted to find gender differences in brain activation of the Nacc and associated structures of the mesolimbic dopamine system during the dilemma. Moreover, based on our previous observation of pronounced interindividual differences in the dilemma-related prefrontostriatal connectivity that varied with the expression of trait impulsivity (Diekhof and

Gruber, 2010; Diekhof et al., in press), which is considered as a direct marker of central dopaminergic transmission capacity (Buckholtz et al., 2010; Zald et al., 2008), we also expected to find a gender dimorphism in the functional connectivity between the right Nacc and the left avPFC.

For the purpose of the present study we examined two groups of healthy male and female subjects. Participants were pre-selected from a larger cohort of 125 undergraduate students, who took part in a neurogenetic study in our laboratory. Female and male subjects were strictly matched

Table 1 – Personality scores, behavioral performance and demographic characteristics of the participants ($n=32$).

	Women ($n=16$)	Men ($n=16$)	p-value*
Age in years (Mean±sem)	24.3±.4	24.7±.6	.554
TCI-novelty seeking (Mean±sem)	20.4±1.3	18.4±1.4	.297
TCI-harm avoidance (Mean±sem)	12.8±1.0	12.2±.9	.681
TCI-reward dependence (Mean±sem)	15.8±.7	15.3±.7	.632
TCI-persistence (Mean±sem)	4.7±.6	4.7±.6	1.000
Absolute number of goal failures (Mean±sem)	4.8±.5	5.4±.5	.355
Percentage of correctly accepted conditioned (rewarding) stimuli in "desire context" in % (Mean±sem)	92.8±1.8	86.1±3.3	.084
Percentage of correctly rejected conditioned (rewarding) stimuli in "reason context" in % (Mean±sem)	97.5±.7	97.4±.8	.938
Reaction times for correct bonus acquisition in "desire context" in ms (Mean±sem)	518±15	497±8	.215
Reaction times for correct rejection of conditioned (rewarding) stimuli in "reason context" in ms (Mean±sem)	499±14	489±13	.592

* Two-tailed significance was determined by a t-test for independent groups.

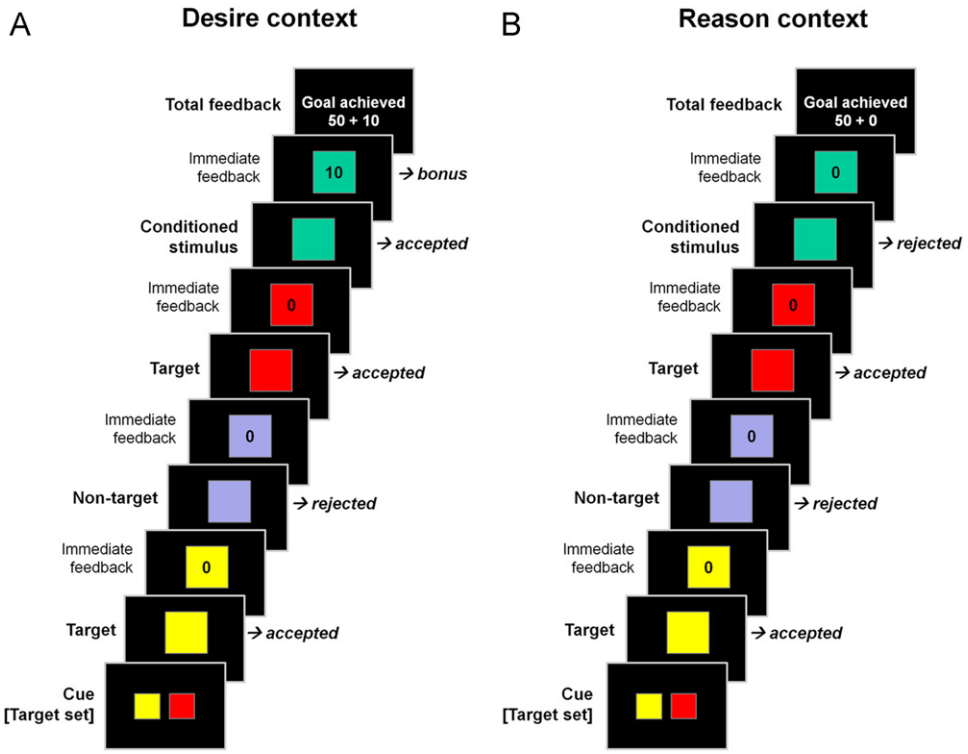

Fig. 1 – *Experimental design of the self-control task.* (A) Example of a task block performed in the 'desire context': In this context subjects were required to select all targets and had to reject all neutral non-targets. They were further free to select the conditioned (rewarding) non-targets (i.e., to follow previously acquired stimulus–response–reward associations) to acquire bonuses during pursuit of the superordinate long-term task goal. (B) Example of a task block performed in the 'reason context': in this context subjects had to select all targets and had to reject all neutral non-targets. In addition, participants always had to reject the conditioned (rewarding) non-targets in this context, which was contrary to the requirements in the 'desire context'. This led to a 'desire-reason dilemma' during which participants had to counteract the behavioral bias oriented towards predictors of immediate reward to achieve the superordinate long-term task goal.

for age, behavioral performance in our self-control task, and personality characteristics (i.e., novelty seeking, harm avoidance, reward dependence and persistence) (see Table 1). Through the close matching for these characteristics it became highly unlikely that the neurophysiological gender differences detected were caused by any of these factors.

2. Results

Firstly, we tested whether reward-related activation in a priori brain regions of the mesolimbic dopamine system (i.e., the Nacc and VTA) may be significantly modulated by the 'desire-reason dilemma' (i.e., during the rejection of conditioned (rewarding) stimuli in the reason versus the desire context; Fig. 1; see also Diekhof and Gruber, 2010; Diekhof et al., 2011). In the two-way ANOVA we found that activation in the Nacc and the VTA was indeed modulated by experimental context (Table 2). The direction of this main effect was subsequently determined by a post-hoc *t*-contrast, which demonstrated a significant reduction of reward-related activation during the 'desire-reason dilemma', when this situation was compared to bonus acquisition in the desire context (Table 3, Fig. 2).

Secondly, we also wanted to examine whether this modulation of reward-related activation by experimental context (reason versus desire context) varied with the factor 'brain gender' (male versus female). However, we found no significant interaction between gender and context in the activation of the Nacc and VTA, not even when lowering the statistical criterion to $p<.05$, uncorrected. Instead, a significant interaction of 'gender by context' was observed in several other regions that are also part of the brain's extended reward system. These regions comprised the right ventral pallidum, the pregenual and adjacent subgenual ACC, the right putamen and the left posterior orbitofrontal cortex (pOFC) as well as two additional clusters in the temporal cortex (Table 4). Importantly, only men showed a significant decrease of activation in these brain areas when rejecting the

Table 2 – Main effect of experimental context in the Nacc and VTA in the two-way ANOVA.

Region	MNI-coordinates (z-value)
L/R Nacc	−12 12 0 (4.38)
	12 12 0 (4.32)
L/R VTA	−9 −24 −12 (3.26)
	9 −21 −18 (3.29)

Activations are reported at $p<.05$, SVC, (for the SVC we used spheres with a radius of 3 mm, around the maxima reported by Diekhof and Gruber, 2010).

Table 3 – Regions of the mesolimbic dopamine system that showed a reduced response during rejection of conditioned (rewarding) stimuli in the "reason context" compared to bonus acquisition in the "desire context" (t-contrast).

Region	Reduced activation during the 'desire-reason dilemma' MNI-coordinates (z-value)
L/R Nacc	−12 12 0 (−4.53)
	12 12 0 (−4.48)
L/R VTA	−9 −24 −12 (−3.45)
	9 −21 −18 (−3.48)

Activations are reported at $p<.05$, SVC, (for the SVC we used spheres with a radius of 3 mm, around the maxima reported by Diekhof and Gruber, 2010).

Table 4 – Interaction of gender by context in the two-way ANOVA of task-related brain activation.

Region	MNI-coordinates (z-value)
R inferior temporal pole	42 6 −45 (3.85)
R ventral pallidum	30 −9 −6 (3.62)
L/R pgACC/sgACC	−6 27 −3 (3.62)
R putamen	24 18 −3 (3.60)
	24 12 −12 (3.33)
L posterior OFC	−36 24 −24 (3.49)
L superior temporal sulcus	−51 −18 −3 (3.43)

Activations are reported at $p<.001$, uncorrected if not otherwise indicated.

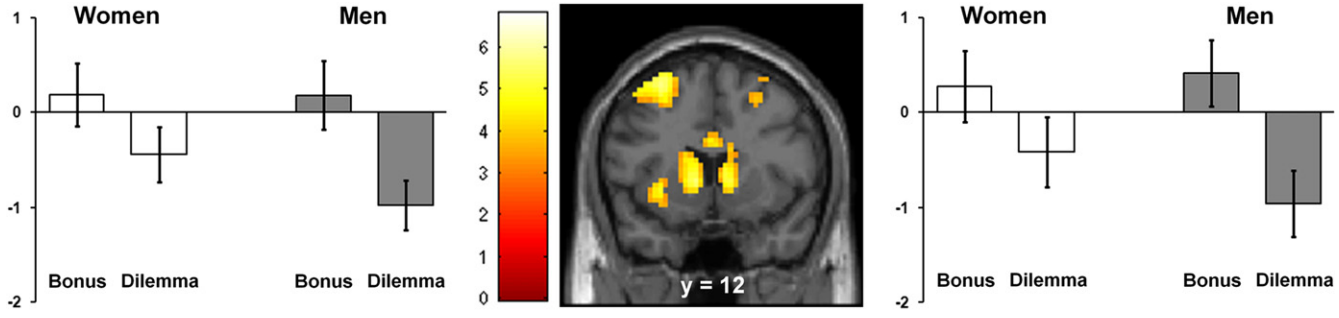

Fig. 2 – *Down-regulation of reward-related ventral striatal activation during the 'desire-reason dilemma'*. A significant down-regulation of activation in the left and right Nacc during the 'desire-reason dilemma' was observed in both sexes. Dilemma-related deactivations are displayed on a coronal slice of the MNI template (activation was thresholded at $p<.001$, uncorrected). The bar graphs show the gender-specific mean parameter estimates for the reward signal in the right Nacc (in the comparison against implicit baseline) during bonus acquisition in the 'desire context', and during a dilemma, which required a rejection of the (same) conditioned stimulus in the 'reason context' (the Y-axis displays the size of the parameter estimates in arbitrary units). Error bars depict the standard error of the mean.

Table 5 – Brain regions that showed a stronger decrease of reward-related activation during rejection of conditioned (rewarding) stimuli in the "reason context" compared to bonus acquisition in the "desire context" (t-contrast).

Region	Stronger decrease of activation during the "desire-reason dilemma" in men > women MNI-coordinates (z-value)	Reduced activation during a "desire-reason dilemma" in women only MNI-coordinates (z-value)	Reduced activation during a "desire-reason dilemma" in men only MNI-coordinates (z-value)
R inferior temporal pole	42 6 −45 (−4.01)	n.s.	42 12 −45 (−3.14)
R ventral pallidum	30 −9 −6 (−3.80)	n.s.	27 −9 −3 (−3.47)
L/R pgACC/sgACC	−6 27 −3 (−3.79)	n.s.	−6 33 3 (−4.08)
R putamen	24 18 −3 (−3.78) 24 12 −12 (−3.52)	n.s.	24 18 −3 (−4.37)
L posterior OFC	−36 24 −24 (−3.67)	n.s.	−36 24 −24 (−4.32)
L superior temporal sulcus	−51 −18 −3 (−3.61)	n.s.	n.s.

Activations are reported at $p<.001$, uncorrected if not otherwise indicated.

conditioned (rewarding) stimuli during a 'desire-reason dilemma' (Table 5, Fig. 3).

To further test the hypothesis that biological sex may modulate the connectivity between the right Nacc and the left avPFC during the successful deployment of self-control, we also performed a PPI analysis using the right Nacc as seed area (see also Diekhof and Gruber, 2010 and Diekhof et al., 2011 for a similar procedure). This PPI analysis further revealed that the functional connectivity between the Nacc and avPFC was indeed modulated by both gender and context (MNI-coordinates (z-value) from the two-way ANOVA: 24 51 0 (3.08); significant at $p<.05$, SVC-corrected). Post-hoc *t*-contrasts showed that this interaction effect was driven by context-related changes in functional connectivity, with opposite directions in both groups (Table 6). While men showed a consistent increase in the connectivity between the right Nacc and the left avPFC during the 'desire-reason dilemma', women rather exhibited the expected negative functional interaction during the dilemma (see Diekhof and Gruber, 2010; Diekhof et al., in press) albeit less consistently across group. When plotting individual parameter estimates from the PPI analysis it became obvious that approximately half of the female subjects displayed a negative connectivity, while the other half exhibited rather positive parameter estimates. Conversely, the majority of male subjects displayed a positive connectivity during the 'desire-reason dilemma' (see Fig. 4). This may help to explain why the more negative dilemma-related connectivity observed in female subjects was less consistent and why we were unable to replicate the original finding by Diekhof and Gruber (2010) as a main effect of context.

For completeness we also report the remaining results of the factorial analysis, which are only of minor importance for the question under research. Accordingly, the two-way ANOVA revealed a significant main effect of gender in the left superior temporal sulcus (MNI-coordinates (z-value): 48-6-15 (3.43); significant at $p<.001$, uncorrected), which was primarily driven by increased activation in this brain region in women when compared to men (MNI-coordinates (z-value) from the post-hoc t-contrast: 48-6-15 (3.61); significant at $p<.001$, uncorrected).

Secondly, we also tested for a main effect of experimental context (reason versus desire context) outside of the Nacc and VTA. Several brain regions implicated in reward-related processing and attentional control showed context-related changes in task-related activity. Among these were the superior colliculus, the inferior temporal cortex the mid cingulate cortex, the superior parietal lobule (SPL) and intraparietal cortex, the superior and inferior frontal cortex, the insula, thalamus and the caudate nucleus (IOG) (Table 7). Post-hoc *t*-contrasts revealed that this main effect was the result of a significant reduction of activation in all of these regions in the 'reason context' (i.e., during the 'desire-reason dilemma') when compared to the 'desire context' (Table 8).

3. Discussion

In this functional neuroimaging study we explored the impact of gender on the neural capacity to counteract impulsive desires. In line with previous evidence on the effects of biological sex on human brain function (Arnold, 2004; Cahill, 2006; Cosgrove et al., 2007; Hines, 2010) the present results demonstrate gender differences in the neural mechanisms mediating choice behavior in a sequential forced choice task. We found that despite similar behavioral performance, age and personality characteristics (Table 1), men and women recruited somewhat different brain regions to resolve the 'desire-reason dilemma'. Accordingly, only male subjects exhibited a context-sensitive decrease in activation of some brain regions that have previously been implicated in behavioral control and affective processing during reward-related decision making (see Tables 4 and 5; Fig. 3). In addition, the connectivity between the Nacc and the avPFC during the dilemma was increased in the male group, but was negative in the female group (Table 6; Fig. 4), despite a similar reduction of reward-related activation in the Nacc in both sexes (Tables 2 and 3; Fig. 2; see also Diekhof and Gruber, 2010). However, from the present study, we cannot rule out that these latter gender differences in prefrontostriatal connectivity were in part caused by an increased inhomogeneity of the female sample, since nine of the female participants, who did not take hormonal contraception, were not synchronized for menstrual cycle phase. Collectively, the present data show that biological sex matters to some extent when

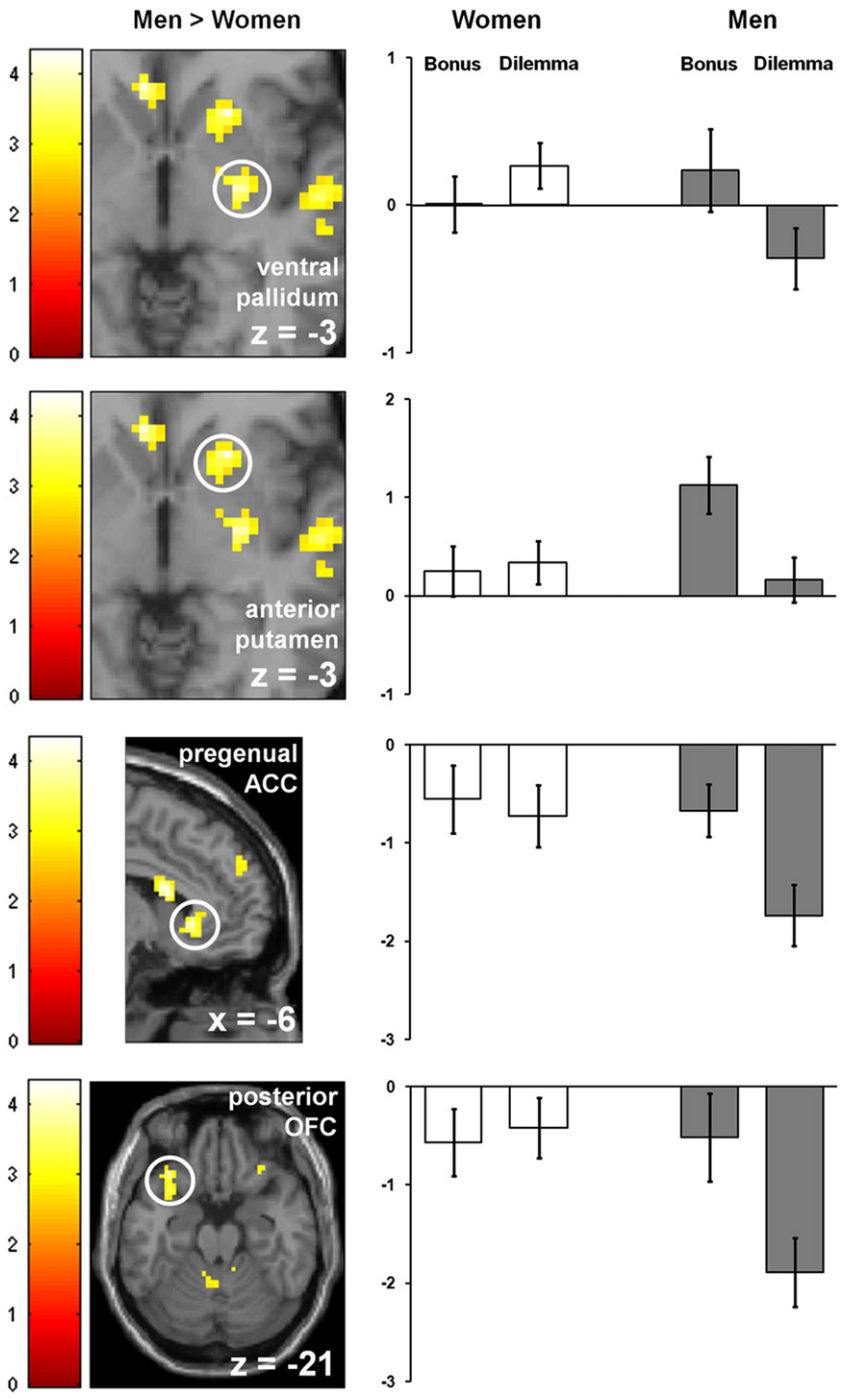

Fig. 3 – *Gender dimorphism in the down-regulation of reward-related activation during the 'desire-reason dilemma'*. A significant down-regulation of activation in the right ventral pallidum, the right anterior putamen, the pregenual ACC and the left pOFC during the 'desire-reason dilemma' could only be observed in men. Dilemma-related deactivations are displayed on slices of the MNI template (for display purposes activation was thresholded at $p < .005$, uncorrected). The bar graphs show the gender-specific mean parameter estimates for the reward signal in the brain regions displayed on the left (in the comparison against implicit baseline). Activations are shown for the 'desire context', in which the conditioned (rewarding) stimulus was selected when it occurred as a non-target, and during a 'desire-reason dilemma', which required a rejection of the (same) conditioned stimulus in the 'reason context' (the Y-axis displays the size of the parameter estimates in arbitrary units). Error bars depict the standard error of the mean.

assessing the neural underpinnings of one specific aspect of the ability to deploy self-control. Yet, our study also demonstrates that (1) these gender effects may be small when comparing performance-matched groups and that (2) potentially confounding factors like menstrual cycle phase need to be controlled in order to achieve unequivocal results.

Table 6 – Functional connectivity between the right Nacc and left avPFC during the "desire–reason dilemma" (t-contrast).

Region	Reduced interaction with right Nacc during a "desire-reason dilemma" in women > men MNI-coordinates (z-value)	Reduced interaction with right Nacc during a "desire-reason dilemma" in women only MNI-coordinates (z-value)	Increased interaction with right Nacc during a "desire-reason dilemma" in men only MNI-coordinates (z-value)
L avPFC	−24 51 0 (−3.28)	−39 45 9 (−2.48)[1]	−24 51 0 (3.70)

Activations are reported at $p<.05$, SVC (for the SVC we used spheres with a radius of 6 mm around the maxima reported by Diekhof and Gruber, 2010). Activation was significant $p<.01$, uncorrected.

3.1. *Gender differences in the down-regulation of reward-related activation during the 'desire-reason dilemma'*

Previous evidence suggests significant organizational and activational effects of gonadal hormones and sex chromosomes on brain structure and function in general (Arnold, 2004; Cahill, 2006) and on the functionality of the mesolimbic dopamine system in particular (Becker, 1999; Dreher et al., 2007; Hedges, Staffend, Meisel, 2010). Our data show that the activation of the Nacc and the VTA to context-manipulations in the present self-control task appeared to be similar in male and female subjects (Table 3, Fig. 2). Thus, the proposed gender-differences in striatal dopaminergic synthesis capacity at rest and following pharmacological challenge (Pohjalainen et al., 1998; Becker, 1999; Lavalaye et al., 2000; Mozley et al., 2001; Laakso et al., 2002) in this closely matched sample apparently did not affect individual reward-related activation in core regions of the ascending mesolimbic dopamine system. Nevertheless, the two matched groups showed a differential activation pattern in neural structures that are functionally associated with the Nacc and VTA. Accordingly, only male subjects exhibited a significant reduction of activation in the ventral pallidum, the putamen, the pgACC/sgACC, the pOFC and in temporal association cortices during the successful resolution of the 'desire-reason dilemma' (Table 5, Fig. 3). These brain regions have previously been associated with action control in the context of reward processing (e.g., Schultz, 2000; O'Doherty, 2004; Haber and Knutson, 2010) or have been implicated in the representation of perceived pleasantness and positive affect (e.g., Grabenhorst, Rolls, Parris, 2008; Wacker, Dillon, Pizzagalli, 2009). One may therefore assume that the observed decrease of activation in these regions during the 'desire-reason dilemma' possibly reduced interference between the suboptimal predictors of immediate reward (i.e., the conditioned rewarding non-targets) and the superordinate long-term goal. This could have been achieved by either attenuating both reflexive approach tendencies and attention to these stimuli or by reducing positive feelings elicited by the predictors of immediate reward. These assumptions are supported by evidence from animal studies, which already suggests that the anterior putamen and the ventral pallidum – the chief output target of the Nacc – mediate incentive motivation and experienced pleasure and also guide goal-directed motor actions towards immediate reward maximization (Hollerman, Tremblay, Schultz, 1998; Cromwell and Schultz, 2003; Hong and Hikosaka, 2008; Berridge et al., 2010; Ikemoto, 2010). Similarly, in humans increased activation of these brain regions has been observed during the anticipation of immediate reward (Knutson et al., 2001a,b, 2005; Kirsch et al., 2003; Croxson et al., 2009; Luo et al., 2009). Importantly, Dreher et al. (2007) found that the male putamen may be more responsive to predictors of reward by demonstrating a higher reward-related anticipatory response in men than in women (Dreher et al., 2007). The present observation of a significant decrease of brain activation during the rejection of the conditioned (rewarding) stimuli during the 'desire-reason dilemma' thus strongly implies that a downregulation of the putamen and the ventral pallidum could have reduced the desire to collect the suboptimal predictor of reward (i.e., the conditioned rewarding non-target) in the male sample. Moreover, the human pOFC has been implicated in the evaluation of behavioral significance of salient environmental stimuli in general and of rewards in particular (Elliott et al., 2000, 2004; Kringelbach and Rolls, 2004; Schnider et al., 2005; Diekhof et al., 2009, 2011; Gruber et al., 2010) and the ventromedial frontal region that includes parts of the medial OFC, the sgACC and adjacent pgACC has been associated with the representation of positive affect and immediate reward value (Zubieta et al., 2003; van den Bos et al., 2007; Grabenhorst, Rolls, Parris, 2008). In men, reward-related activation in the OFC has been found to be more pronounced whilst processing gender-specific motivationally salient cues (e.g., attractive facial displays of the opposite sex, Cloutier et al., 2008) or during successful performance of tasks that are often preferred by males (e.g., computer games; Hoeft et al., 2008). A dilemma-related reduction of activation in these frontal regions thus could have mirrored the stronger need for a devaluation of the rejected immediate rewards in the 'reason context' (see also Diekhof et al., in press), which could have further promoted the successful resolution of the 'desire-reason dilemma'. In that way, the present findings of differential brain activation in men despite similar behavioral performance may also fit well with the idea that most gender differences in brain function may be compensatory (see next section for further discussion of this possibility).

3.2. *Is the observed gender difference in the dilemma-related prefrontostriatal connectivity compensatory?*

Although the present data of a small gender difference in the recruitment of various regions of the reward system are in line with previous observations from neuroimaging studies (see above), they do not explain the origin of these differences. Gender differences in the functional neural architecture can arise from early influences of gonadal hormones or of sex chromosomes on brain structure (Goldstein et al., 2001; Hines, 2011), or may be rather activational in nature (e.g., are

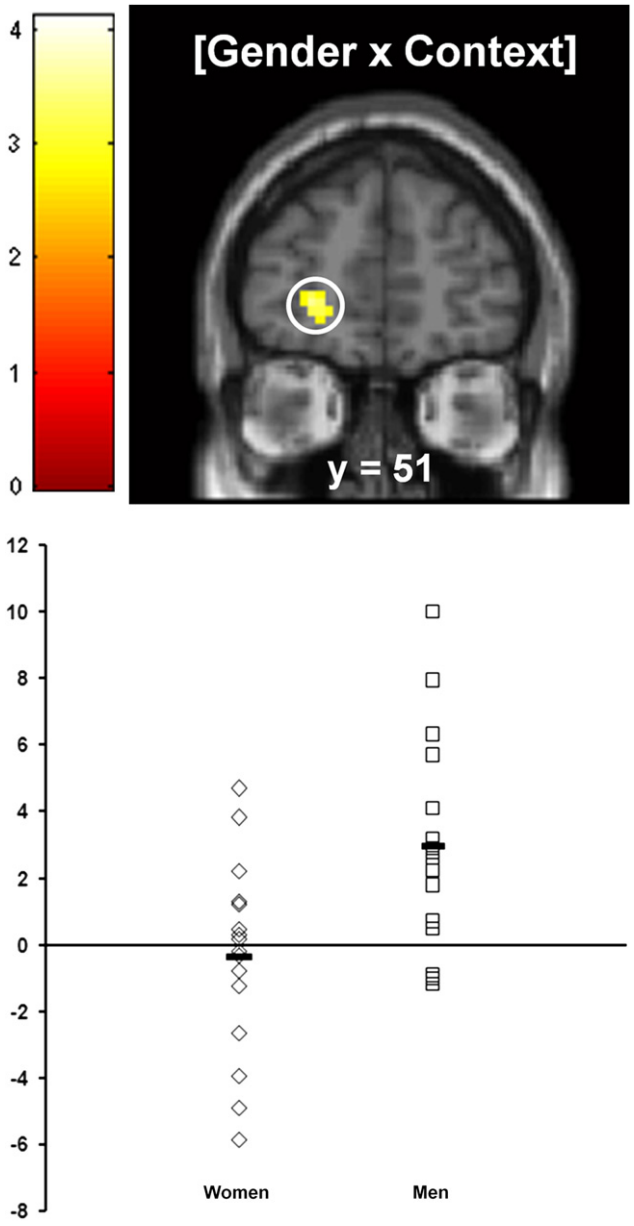

Fig. 4 – *Gender dimorphism in the context-related change in prefrontostriatal connectivity during the 'desire-reason dilemma'*. While women exhibited a non-significant decrease in the connectivity between right Nacc and left avPFC during the dilemma, men exhibited a positive functional coupling between these regions when successfully rejecting predictors of immediate rewards during pursuit of the long-term goal. The region in the left frontomarginal sulcus of the avPFC, whose connectivity with the right Nacc showed an interaction between gender and context, is displayed on a coronal slice of the MNI template (for display purposes activation was thresholded at $p<.005$, uncorrected). Individual parameter estimates reflecting subject-specific differences in prefrontostriatal connectivity strength from the direct comparison of [dilemma versus desire] are further plotted for each gender separately (the Y-axis displays the size of the parameter estimates in arbitrary units). Horizontal bars display the arithmetic mean for each of the two groups.

Table 7 – Main effect of context in the remaining brain regions in the two-way ANOVA of task-related brain activation.

Region	MNI-coordinates (z-value)
L/R inferior temporal gyrus	−54 −48 −15 (5.32)*
	54 −48 −18 (5.71)*
L/R superior colliculus/thalamus	0 −24 −3 (5.58)*
L caudate nucleus	−9 15 6 (4.86)*
	−9 9 12 (4.50)
L/R thalamus	−6 −12 −3 (4.72)*
	9 −3 −6 (4.35)
L/R mid cingulate cortex	0 −3 33 (5.49)*
L/R superior frontal sulcus/middle frontal gyrus	−27 18 60 (5.39)*
	30 27 57 (4.61)*
L/R inferior frontal sulcus/gyrus	−39 45 9 (4.74)*
	45 45 15 (5.22)*
L/R central orbitofrontal cortex	−27 45 −12 (3.93)
	27 39 −12 (3.94)
L/R SPL/intraparietal cortex	−48 −54 54 (5.27)*
	−30 −57 45 (4.38)
	33 −63 51 (5.17)*
	51 −39 48 (4.55)
R IOG	42 −87 −9 (4.78)*
	30 −96 −6 (3.19)
L/R insula	−30 15 −3 (4.70)*
	33 18 −6 (4.11)
L central sulcus/postcentral gyrus	−39 −24 60 (4.10)
L/R DMPFC	3 45 54 (4.06)
R anterior OFC	39 51 −12 (3.78)
L posterior insula	−45 −21 24 (3.66)
	−39 −9 15 (3.27)
L/R cerebellum	−3 −51 −12 (3.48)
R inferior temporal gyrus	57 −24 −27(3.40)
	54 −15 −33 (3.26)
L paracentral lobule	−9 −36 69 (3.39)
L IFJ	−42 6 30 (3.20)
L pregenual ACC	−3 42 12 (3.13)
L/R PCC	0 −30 36 (3.10)

Activations are reported at $p<.001$, uncorrected if not otherwise indicated.
* $p<.05$, FWE-corrected for whole brain.

driven by fluctuating gonadal hormones in adult pre-menopausal women, like in the study by Dreher et al., 2007). Further, gender differences in task-related enthusiasm (Hoeft et al., 2008) and in regional size (e.g., the putamen and globus pallidus may be bigger in men than in women (Rijpkema et al., 2012)) could also contribute to differences in task-related activation (e.g., by increasing the signal-to-noise ratio in these regions). Since the present study did not control for the size of subcortical brain regions, individual task engagement or concentrations of gonadal hormones we cannot be sure which aspect originally drove the present results. In fact, the observation of an increased variance in the direction of the dilemma-related prefrontostriatal connectivity in women compared to men (see Fig. 4) could have been caused by cycle-dependent fluctuations in steroid hormones (e.g., estradiol) that are known to interact with the dopaminergic system and the associated brain structures (e.g., Becker, 1999). Finally, it is also possible that part of the observed gender differences may have been compensatory in

Table 8 – Regions outside of the mesolimbic dopamine system that showed a reduced response during rejection of conditioned (rewarding) stimuli in the "reason context" compared to bonus acquisition in the "desire context" (t-contrast).

Region	Reduced activation during the 'desire-reason dilemma' MNI-coordinates (z-value)
L/R inferior temporal gyrus	−54 −48 −15 (−5.45)*
	54 −48 −18 (−5.83)*
L/R superior colliculus/ thalamus	0 −24 −3 (−5.70)*
L caudate nucleus	−9 15 6 (−5.00)*
	−9 9 12 (−4.65)*
L/R thalamus	−6 −12 −3 (−4.86)*
	9 −3 −6 (−4.50)
L/R mid cingulate cortex	0 −3 33 (−5.61)*
L/R superior frontal sulcus/middle frontal gyrus	−27 18 60 (−5.51)*
	30 27 57 (−4.75)*
L/R inferior frontal sulcus/ gyrus	−39 45 9 (−4.87)*
	45 45 15 (−5.35)*
L/R central orbitofrontal cortex	−27 45 −12 (−4.09)
	27 39 −12 (−4.10)
L/R SPL/intraparietal cortex	−48 −54 54 (−5.40)*
	−30 −57 45 (−4.53)
	33 −63 51 (−5.29)*
	51 −39 48 (−4.69)*
R IOG	42 −87 −9 (−4.92)*
	30 −96 −6 (−3.39)
L/R insula	−30 15 −3 (−4.84)*
	33 18 −6 (−4.27)
L/R DMPFC	3 45 54 (−4.22)
R anterior OFC	39 51 −12 (−3.95)
L/R cerebellum	−3 −51 −12 (−3.67)
R inferior temporal gyrus	57 −24 −27(−3.58)
	54 −15 −33 (−3.45)
L IFJ	−42 6 30 (−3.39)
L pregenual ACC	−3 42 12 (−3.32)
L/R PCC	0 −30 36 (−3.30)

Activations are reported at $p<.001$, uncorrected if not otherwise indicated.
* $p<.05$, FWE-corrected for whole brain.

nature or could have reflected gender-specific cognitive strategies. It has already been assumed that gender differences in brain function or structure may prevent sex differences in overt behavior by compensating for organizational and/or activational differences in the brain (De Vries, 2004). Similar to our previous study, which compared highly impulsive and extremely controlled individuals (Diekhof et al., in press) in the present study the two groups did not differ in their overall behavioral performance (Table 1) and received a similar amount of training on the day before the actual MR scan took place. Still, male and female subjects showed a differential activation pattern in some regions of the brain's reward system (Fig. 3) as well as marked differences in the prefrontostriatal connectivity during the 'desire-reason dilemma' (Fig. 4). On the one hand, these observations may fit well with the theory of a compensatory recruitment of task-relevant brain mechanisms. It is well known that if psychiatric patients are able to compensate for behavioral impairments (e.g., in the *n*-back task) they show an increased recruitment of task-relevant brain regions in comparison to normal subjects (see for example Manoach, 2003). One could therefore imagine that the opposite may happen when activation in certain brain regions interferes with the current task (i.e., activation in task irrelevant brain regions may be more strongly reduced when subjects successfully compensate for an internal predisposition). In the present study, only men showed a significant decrease in activation of the extended reward system during the rejection of immediately rewarded stimuli (see Fig. 3). One could therefore speculate that increased activation in these 'impulsive' brain regions in men may have interfered with the successful resolution of the desire-reason dilemma, which thus required a 'male-specific' compensatory down-regulation. On the other hand, behavioral compensation can also be achieved by the recruitment of specific cognitive strategies. For example, if a subject was highly distracted by the colors promising an immediate outcome in the 'reason context', he/she might have tried to (un)consciously work against the corruption by the stimulus-response-reward contingency, which could have altered the overall connectivity between brain regions in the whole experiment. As we did not debrief our subjects directly after testing, we can only speculate about the use of different cognitive strategies by the two sexes. However, the somewhat unexpected observation of a more positive connectivity between avPFC and Nacc in the male sample, which was at odds to our original finding (Diekhof and Gruber, 2010), may point in this direction. In fact, the present observation is highly reminiscent of a finding made in a population of highly controlled subjects, who apparently also used a different cognitive strategy than a sample of highly impulsive subjects (see Diekhof et al., in press). Similar to our male sample these controlled subjects also did not show the expected negative prefrontostriatal connectivity during the desire-reason dilemma, but still performed equally well as the comparison group. For this reason one could likewise speculate that by using a 'male-specific' cognitive strategy that altered the prefrontostriatal connectivity in the 'reason context', men may have been equally effective as women in controlling their desire for immediate reward.

Given the potential confounds and limitations of the present study (see also Section 3.4) we cannot be sure, which of these alternative explanations mainly accounts for the present observations. Future studies are certainly needed to assess in more detail to what extent factors like gender differences in brain structure (e.g., regional size), dopaminergic synthesis capacity, cycle-dependent fluctuations in gonadal hormones that affect catecholamine concentrations, gender-specific compensatory mechanisms or task-related cognitive strategies influence regional brain activation and connectivity in behaviorally matched gender groups.

3.3. *Regional brain activation modulated by either context or gender per se*

There were several brain regions that showed a significant decline in activation independent of gender when comparing optimal decisions during the 'desire-reason dilemma' (i.e., the rejection of immediate reward for the higher-order

long-term goal) with optimal choices in the 'desire context' (i.e., bonus acquisition) (Tables 7 and 8). Among these were the Nacc and the VTA, whose dilemma-related down-regulation may have been a necessary prerequisite to counteract the desire for immediate reward in the present self-control task as had been demonstrated earlier (see Diekhofand Gruber, 2010; Diekhof et al., in press). In addition, a significant change in activation between the 'desire-context' and the 'reason-context' was also observed in several other brain regions, which have previously been implicated in the processing of salient, motivationally significant stimuli that demanded an immediate adjustment of goal-directed behavior (e.g., Gruber et al., 2009; Diekhof et al., 2011). In that way, one may assume that areas like the superior colliculus or the intraparietal cortex may have promoted the rapid orientation of attention towards the salient conditioned (rewarding) colors in the 'desire context'. Notably, the absence of a modulation by gender in any of these brain regions further suggests that the function of these brain regions probably was rather basic in the task at hand and supposedly organized in a comparable way in both sexes. However, this does not rule out that when using a more homogeneous female sample (e.g., a sample constituting exclusively women in the mid luteal or premenstrual phases) a functional gender-dimorphism would have been observed, at least in brain areas of the mesolimbic reward system (see for example Dreher et al., 2007; Ossewaarde et al., 2010).

Finally, we also identified one brain area that exhibited a modulation by gender above any main effect of cognitive context. We can only speculate that the increase in activation in the left superior temporal sulcus of the female subjects may have originated from a more profound, presumably organizational gender dimorphism. There is already evidence that the temporal cortex may have a lower synaptic density in human women than in men (Alonso-Nanclares et al., 2008), which could differentially influence the efficiency with which certain cognitive operations are performed. However, the present activation cluster was relatively small (i.e., 8 voxels in the *F*-contrast of the main effect, and 19 voxels in the *t*-contrast) and the activation did not survive a whole-brain correction for familywise error. Therefore, future studies are needed to replicate this finding and further dip into the functional meaning of this observation.

3.4. *Limitations of the present study*

There are several limitations that need to be taken into account when interpreting the present results:

(a) Statistical effects: activation in brain areas that showed a gender-dimorphic response and connectivity (see Tables 5 and 6) did not survive the whole-brain correction for family-wise error, despite a clear concordance with previous findings (e.g., Diekhof and Gruber, 2010; Diekhof et al., in press). The fact, that the two groups of healthy subjects were strictly matched for behavioral performance and personality characteristics may in part account for the small statistical effects. Importantly, to our knowledge this is the first neuroimaging study that compared male and female groups, who were also matched for TCI personality characteristics. From our previous study (Diekhof et al., in press) we already knew that differences in trait impulsivity may significantly affect brain physiology despite comparable behavioral performance. In the present study we could be sure that the observed gender effects were not confounded by group-specific differences in these personality traits. Nevertheless, it is also possible that the strict matching could have in turn reduced gender differences in brain activation when compared to other studies that did not control for this confound.

(b) Sample size: one also has to be aware of the fact that only one out of four participants (i.e., 32 out of 125 subjects from the larger sample) could be included in the present study to achieve such a close matching for personality characteristics and performance data. Even though it would have been desirable to enlarge the available pool of participants, this was not possible at the time of the study. Therefore the present data are based on a relatively small sample (i.e., 16 individuals in each group), even though the number of participants is still sufficient for a reliable fMRI analysis. In combination with the strict matching criteria this may further explain why the observed gender differences were quite small.

(c) Control of menstrual cycle phase: in addition to the above described limitations, fluctuations in gonadal hormones over the menstrual cycle could have further equalized functional differences between the two samples. One could imagine that for instance during menses, when the concentration of female sexual hormones (i.e., estradiol and progesterone) is low, women might have exhibited a more 'male-like' functional architecture than in the luteal phase. As already outlined above the failure to synchronize testing of the female sample could have significantly increased the heterogeneity in this group and thus could have rendered functional gender differences smaller than they actually were.

For these reasons, future studies are needed to further substantiate the present findings and interpretations. Importantly, researchers should preconceive three aspects before even starting a gender project: (1) Participants need to be closely matched for subject-specific characteristics like personality traits and behavioral performance that may in themselves produce functional differences in the human brain. (2) Large sample sizes are supposedly needed to demonstrate significant effects as a function of gender, since particularly in populations that are closely matched for various characteristics gender differences are expected to be small. (3) Female subjects should be synchronized with regard to menstrual cycle phase or should at least take contraceptive medication to avoid unnecessary heterogeneity in the female sample. Finally, one should not forget that there might be many other factors that could also influence the results of gender comparisons and affect regional brain activation. These include gender-specific preferences (e.g., men might be more engaged by exciting computer games than women, which could by itself lead to stronger reward-related activation; Hoeft et al., 2008) or differences in the size

of certain brain structures (e.g., Rijpkema et al., 2012), which could influence the signal-to-noise ratio in functional analyses. These factors cannot always be controlled for and researchers should be aware of these potential confounds that could limit the interpretability of their results.

4. Conclusion

Collectively, the present findings support the view that men and women differ in the neural mechanisms that enable them to successfully control their desire for immediate reward. Activation in several cortical and subcortical brain regions implicated in reward and motivation showed a small gender dimorphism, with male subjects exhibiting a more pronounced down-regulation of reward-related activation during the 'desire-reason dilemma'. Further, men exhibited a more positive prefrontostriatal coupling when they had to forego an immediate reward for the higher-order long-term goal. Importantly, these functional differences were observed despite a strict matching of the two groups for age, personality characteristics and behavioral performance suggesting gender-dimorphic most likely compensatory mechanisms. Nevertheless, several limitations preclude an equivocal interpretation of our data. Therefore, controlled future studies are needed to determine whether the present findings indeed mirror organizational and neurofunctional gender differences that manifested in a recruitment of different neural resources, or whether men and women employed different cognitive strategies to cope with the task demands and to compensate for gender-specific shortcomings.

5. Experimental procedures

5.1. *Subjects*

Participants were 32 right-handed healthy undergraduate students (16 females) at the Georg-August-University in Goettingen/Germany. Of these seven female participants indicated that they took hormonal contraception on a regular basis. Subjects only qualified for the study if they did not fulfill any of the following exclusion criteria: (a) previous medical diagnosis of neurological or psychiatric disorders; (b) previous or current use of psychotropic medication (e.g., antidepressants); or (c) any contraindications for an MRI scan (e.g., an implanted cardiac pace maker). The participants of the present study were selected from a sample of 125 undergraduate students that took part in a larger neurogenetic study in our laboratory. Of these 87 subjects met the first inclusion criterion, namely that the number of 'goal failures' in the whole experiment did not exceed a total of 8 failures (for the definition of the term 'goal failure' please see the description of the experimental paradigm below). This large sample provided a sufficient database to allow us to compose the present samples of closely matched male and female individuals, who did not significantly differ with respect to age, personality characteristics and behavioral performance in the self-control task (see Table 1). By closely matching female and male participants we were able to widely rule out that significant differences in personality characteristics, age or task performance may have confounded the observed gender differences in neural activation and connectivity patterns.

Ethical approval from the local ethical committee at the University Medical Center of the Georg August University Goettingen and written-informed consent were obtained prior to the investigation. Subjects were paid for participation.

5.2. *Experimental paradigm*

The experiment started with an *operant conditioning task* that was performed outside of the scanner. During this task subjects learned to associate specific colors and responses with either an immediate reward or a neutral outcome (see also Diekhof and Gruber, 2010). Choice between a left and a right button was free and subjects were encouraged to explore the stimulus-response-reward contingencies to maximize their overall outcome. In all, squares of 8 different colors were presented twenty times each in a randomized sequence. Two of these colors led to an immediate reward (i.e., reward of 10 points) when collected with a left button press. Four colors always led to a neutral outcome regardless of button choice. Selection of the remaining two colors with a left button press led to an immediate loss (i.e., loss of 10 points). These latter two 'potentially punished' colors were included in the conditioning task in order to prevent a behavioral preference for the left response button also in response to the neutral colors, but they were not presented in the following task (see below). In sum, the ultimate goal of the operant conditioning procedure was the establishment of stimulus-response-reward contingencies, which were relevant for the second phase of the experiment.

During the second phase of the experiment, which took part in the MR-scanner, participants performed a modified version of the self-control task introduced by Diekhof and Gruber (2010) (see also Diekhof et al., in press). Stimulus material (i.e., rewarded and neutral colors) remained the same as in the operant conditioning task (except for the 'potentially punished' stimuli, see above). However, in contrast to the conditioning session, in this task subjects had to pursue a superordinate long-term goal during task blocks of 4 or 8 trials to acquire 50 points for successful performance at the end of individual task blocks (see Fig. 1). The superordinate goal of an individual task block was to collect the two target colors that were defined at the beginning of each block. Target colors could occur more than once within a block and had to be collected upon each appearance to reach the goal. Apart from this, subjects also had to incorporate one of two context rules into their decisions, which determined how to treat the remaining non-target colors to successfully finish a block (i.e., to gain 50 points for successful achievement of the superordinate long-term goal). In the *'reason context'* all non-target colors had to be rejected regardless of their immediate reward association to achieve the superordinate goal (Fig. 1B). Conversely, in the *'desire context'* subjects were free to also collect the two conditioned (rewarding) non-target colors for an immediate bonus, whereas all remaining unrewarded non-target colors had to

be rejected (Fig. 1A). Bonuses acquired in the 'desire context' were added to the 50 points at the end of a block, if the long-term goal was successfully reached. Although subjects were free to decide whether to collect or to reject conditioned (rewarding) non-targets in the 'desire context', the optimal strategy for reward maximization was – apart from collecting the targets and rejecting the unrewarded non-targets – to give into the 'desire' to acquire the immediately rewarded non-target colors. Conversely, during the 'reason context' subjects were forced to overcome the behavioral tendency to respond to these conditioned (rewarding) stimuli, which contradicted the superordinate long-term goal. This means that in the latter case, participants had to exert self-control to resolve this 'desire-reason dilemma'.

In both the 'desire' and the 'reason context' the conditioned (rewarding) non-targets as well as the unrewarded non-targets could occur up to 30 times each and goal-relevant target stimuli could appear up to 60 times each in a pseudorandomized sequence with a counterbalanced trial order. Goal failures reduced these numbers, because a failure to implement the long-term goal terminated a block immediately before its actual end with the feedback '*goal failure*'. The consequence of such a goal failure was a loss of the points already acquired within that respective task block. In order to have enough events of the trial types of interest for the subsequent fMRI analysis, we decided to include only subjects with a maximum of 8 goal failures throughout the whole experiment.

In all, the participants completed 40 task blocks over the course of two fMRI runs. Half of the task blocks were performed in the 'desire context' and the 'reason context'. The context always changed after 2 consecutive task blocks, which was indicated by a context cue. Context cues indicating a change in decision context always appeared for 1800 ms (followed by a 200 ms blank screen delay). The appearance of the context cues was synchronized with the scanner signal (i.e., coincided with the beginning of the acquisition of a new volume). Subsequently the two relevant target colors for the upcoming task block were shown for 1500 ms (preceded by a 200 ms blank screen delay and followed by another 200 ms, in which a blank screen was presented). The relevant target colors changed every task block. The display of the two relevant target colors was followed by individual trials, in which subjects had to collect relevant targets and also bonuses in the 'desire context' or only had to collect targets in the 'reason context' (see above; Fig. 1). An individual trial had a duration of 1900 ms. It started with a blank screen (duration=200 ms), before a colored square was shown for 900 ms, which was followed by an immediate feedback for the current choice the subject had made. This feedback had a duration of 700 ms. A trial ended with a blank screen, which was shown for 100 ms. The total feedback, which indicated the overall outcome of a task block (including bonuses), was always presented at the end of the respective task block (for 1800 ms) and was followed by a blank screen of 100 ms before the next task block began or a change in context was indicated. Failure to implement the superordinate task goal or failure to answer within 900 ms led to termination of the current task block and zero outcome (goal failure; see also above). Points acquired in the second part of the experiment were cashed into real money. Subjects could receive up to €30, which were added to the general reimbursement for participation.

5.3. *Assessment of personality characteristics*

Participants completed the German version of the Temperament and Character Inventory (TCI) devised by Cloninger et al. (1993) to determine individual personality characteristics. Temperament has been defined as those components of personality that are heritable and stable throughout life and may also be linked to the functional integrity of different neurotransmitter systems (e.g., Cloninger et al., 1993; Samochowiec et al., 2001; Munafò et al., 2005). The TCI incorporates four temperament traits (novelty seeking, harm avoidance, reward dependence and persistence) and allows assessing differences between individuals in their automatic responses to emotional and motivationally relevant stimuli (e.g., fear, anger, or impulsive behavioral tendencies).

5.4. *FMRI data acquisition and analyses*

Imaging was performed on a 3T system (Magnetom TRIO, Siemens Healthcare, Erlangen, Germany) equipped with the standard eight channel phased-array head coil. First, a *T*1-weighted anatomical dataset at 1 mm isotropic resolution was acquired. For fMRI, thirty-one axial slices parallel to the anterior commissure–posterior commissure line were obtained in ascending acquisition order (slice thickness=3 mm; interslice gap=.6 mm) using a gradient-echo echo-planar imaging (EPI) sequence (echo time of 33 ms; flip angle of 70°; field-of-view of 192 mm; inter-scan repetition time (TR) of 1900 ms).

A total of 370 volumes were acquired in 2 functional runs. Stimuli were viewed through goggles (Resonance Technology, Northridge, USA) during fMRI acquisition and subjects responded via button press on a fiber optic computer response device (Current Designs Inc., Philadelphia, USA). The head was stabilized by small cushions to avoid head movements during scanning. Triggering of the visual stimulation (i.e., triggering of the context cues) by the scanner impulse during functional data acquisition and generation of all stimuli was conducted through the Presentation® Software (Neurobehavioral Systems, Albany, USA).

Functional images were preprocessed and analyzed with SPM5 (Wellcome Department of Cognitive Neurology, University College London, London, UK). Preprocessing comprised coregistration, realignment and unwarping, corrections for slice-time acquisition differences and low-frequency fluctuations, normalization into standard stereotactic space [skull-stripped EPI template by the Montreal Neurological Institute (MNI)], and spatial smoothing with an isotropic Gaussian kernel filter of 9 mm full-width half-maximum.

Statistical analyses used a general linear model (GLM), which comprised eleven independent regressors [i.e., the goal-relevant targets, the neutral non-targets, the conditioned (rewarding) non-targets for the 'desire context' and for the 'reason context', respectively, the two context cues, and finally the block cues and the block feedback for either successful goal completion or overall goal failure].

These onset regressors reflected the average activation to the trials in each condition. Erroneous trials and the conditioned (rewarding) stimuli that were not selected for an immediate bonus in the 'desire context' were excluded from the analyses.

A vector representing the temporal onsets of stimulus presentation was convolved with a canonical hemodynamic response function (hrf) to produce the predicted hemodynamic response to each experimental condition. Linear *t* contrasts were defined for assessing the specific effects elicited by the conditioned (rewarding) non-targets in the two contexts. Single-subject contrast images were taken to the second level to assess group effects with random-effects analyses. We used a two-way ANOVA with the factors 'gender' (female versus male) and 'context' (desire versus reason) to determine the associated main effects as well as significant interactions between factors. Post-hoc *t*-tests were then used to test for specific differences between men and women in brain activation modulated by a 'desire-reason dilemma'.

The standard statistical criterion for group statistics was $p<.001$, uncorrected. For the Nacc and VTA, that had been found to be downregulated during the 'desire-reason dilemma' (Diekhof and Gruber, 2010), we used small-volume-corrections (SVC; Worsley et al., 1996). These applied to spherical volumes (radius = 3 mm) at the activation maxima in the left and right Nacc (MNI-coordinates: −12 12 −3/ 12 12 −3) and in the left and right VTA (MNI-coordinates: −8 −20 −12/ 8 −20 −16). Activations corrected for small volume are reported at a threshold of $p<.05$, corrected.

5.5. *Psychophysiological interaction analysis (PPI analysis) (Friston et al., 1997)*

As a replication of Diekhof and Gruber (2010) and Diekhof et al. (in press), we further assessed the functional interaction between the right Nacc and the left avPFC during the 'desire-reason dilemma' (i.e., when the immediate reward contingency and the superordinate goal competed for action control). The local maximum in the right Nacc (MNI-coordinates: 12 12 0), which also showed a significant main effect of context in the present study (see Table 2), was selected as seed area for the PPI analyses (please see Diekhof and Gruber, 2010, for a similar procedure). Individual blood oxygenation level-dependent (BOLD) signal time courses were extracted from this local activation maximum in the respective contrasts (see below), which served as the physiological vector in the PPI analysis. In order to specifically assess the change in functional interaction between the right Nacc and the avPFC during the 'desire-reason dilemma' when compared to the situation, in which subjects were allowed to follow their desire for immediate reward, we calculated two PPI analyses. One of these analyses used the contrast that compared conditioned (rewarding) stimuli presented in the 'reason context' with the implicit baseline as the psychological vector. The other comprised the same contrast (i.e., conditioned (rewarding) stimuli against the implicit baseline) from the 'desire context' as psychological vector. To the two PPI analyses the following procedure applied: using Matlab and SPM5, the hemodynamic signals were first deconvolved using a parametric empirical Bayesian formulation and mean-corrected (Gitelman et al., 2003). Then the PPI term was built separately by multiplying the deconvolved and mean-corrected BOLD signal with the respective psychological vector. After convolution with the hrf, mean correction, and orthogonalization, the three regressors (i.e., PPI term, physiological vector, and psychological vector) went into the statistical analysis to determine context-dependent changes of functional connectivity over and above any main effect of task or any main effect of activity in the corresponding brain areas. Random-effects analyses were performed on single-subject PPI contrast images. We used a two-way ANOVA with the factors 'gender' (female versus male) and 'context' (desire versus reason) that included the two baseline contrasts (see above) for each gender-group to determine the associated main effects as well as significant interactions between factors in the left avPFC. Post-hoc t-tests were used to test for differences in functional interactions between men and women. We also used small-volume-corrections (using spheres with a radius of 6 mm around previously reported maxima in the left avPFC that exhibited a negative interaction with the right Nacc (MNI-coordinates: −28 56 4 and −20 56 4), see Diekhof and Gruber, 2010).

Acknowledgments

We would like to thank Ilona Pfahlert, Britta Perl and Sarah Hescham as well as the staff of the unit 'MR-Research in Neurology and Psychiatry' at the University Medical Center Goettingen (Germany) for help with data acquisition and analysis. We also thank Timo Graen for programming the test protocols.

REFERENCES

Abler, B., Grön, G., Hartmann, A., Metzger, C., Walter, M., 2012. Modulation of frontostriatal interaction aligns with reduced primary reward processing under serotoninergic drugs. J. Neurosci. 32, 1329–1335.

Alonso-Alonso, M., Ziemke, F., Magkos, F., Barrios, F.A., Brinkoetter, M., Boyd, I., Rifkin-Graboi, A., Yannakoulia, M., Rojas, R., Pascual-Leone, A., Mantzoros, C.S., 2011. Brain responses to food images during the early and late follicular phase of the menstrual cycle in healthy young women: relation to fasting and feeding. Am. J. Clin. Nutr. 94, 377–384.

Alonso-Nanclares, L., Gonzalez-Soriano, J., Rodriguez, J.R., DeFelipe, J., 2008. Gender differences in human cortical synaptic density. PNAS 105, 14615–14619.

Arnold, A.P., 2004. Sex chromosomes and brain gender. Nat. Rev. Neurosci. 5, 701–708.

Becker, J.B., 1999. Gender differences in dopaminergic function in striatum and nucleus accumbens. Pharmacol. Biochem. Behav. 64, 803–812.

Berridge, K.C., Ho, C.Y., Richard, J.M., DiFeliceantonio, A.G., 2010. The tempted brain eats: pleasure and desire circuits in obesity and eating disorders. Brain Res. 1350, 43–64.

Best, S.E., Sarrel., P.M., Malison, R.T., Laruelle, M., Zoghbi, S.S., Baldwin, R.M., Seibyl, J.P., Innis, R.B., van Dyck, C.H., 2005. Striatal dopamine transporter availability with [123I]β-CIT SPECT is unrelated to gender or menstrual cycle. Psychopharmacology 183, 181–189.

Buckholtz, J.W., Treadway, M.T., Cowan, R.L., Woodward, N.D., Li, Ansari, M.S., Baldwin, R.M., Schwartzman, A.N., Shelby, E.S., Smith, C.E., Kessler, R.M., Zald, D.H., 2010. Dopaminergic network differences in human impulsivity. Science 329, 532.

Burke, S.M., van de Giessen, E., de Win, M., Schilt, T., van Herk, M., van den Brink, W., Booij, J., 2011. Serotonin and dopamine transporters in relation to neuropsychological functioning, personality traits and mood in young adult healthy subjects. Psychol. Med. 41, 419–429.

Butera, P.C., 2010. Estradiol and the control of food intake. Physiol. Behav. 99, 175–180.

Cahill, L., 2006. Why sex matters for neuroscience. Nat. Rev. Neurosci. 7, 477–484.

Cloninger, C.R., Svrakic, D.M., Przybeck, T.R., 1993. A psychobiological model of temperament and character. Arch. Gen. Psychiatry 50, 975–990.

Cloutier, J., Heatherton, T.F., Whalen, P.J., Kelley, W.M., 2008. Are attractive people rewarding? Sex differences in the neural substrates of facial attractiveness. J. Cogn. Neurosci. 20, 941–951.

Cosgrove, K.P., Mazure, C.M., Staley, J.K., 2007. Evolving knowledge of sex differences in brain structure, function, and chemistry. Biol. Psychiatry 62, 847–855.

Cromwell, H.C., Schultz, W., 2003. Effects of expectations for different reward magnitudes on neuronal activity in primate striatum. J. Neurophysiol. 89, 2823–2838.

Croxson, P.L., Walton, M.E., O'Reilly, J.X., Behrens, T.E., Rushworth, M.F., 2009. Effort-based cost-benefit valuation and the human brain. J. Neurosci. 29, 4531–4541.

De Vries, G.J., 2004. Minireview: sex differences in adult and developing brains: compensation, compensation, compensation. Endocrinology 145, 1063–1068.

Diekhof, E.K., Falkai, P., Gruber, O., 2009. Functional interactions guiding adaptive processing of behavioral significance. Hum. Brain Mapp. 30, 3325–3331.

Diekhof, E.K., Gruber, O., 2010. When desire collides with reason: functional interactions between anteroventral prefrontal cortex and nucleus accumbens underlie the human ability to resist impulsive desires. J. Neurosci. 30, 1488–1493.

Diekhof, E.K., Falkai, P., Gruber, O., 2011. The orbitofrontal cortex and its role in the assignment of behavioural significance. Neuropsychology 49, 984–991.

Diekhof, E.K., Nerenberg, L., Falkai, P., Dechent, P., Baudewig, J., Gruber, O. Impulsive personality and the ability to resist immediate reward: an fMRI study examining interindividual differences in the neural mechanisms underlying self-control. Hum. Brain Mapp., Electronic Publication ahead of Print, http://dx.doi.org/10.1002/hbm.21398, in press.

DiMeo, A.N., Wood, R.I., 2006. Self-administration of estrogen and dihydrotestosterone in male hamsters. Horm. Behav. 49, 519–526.

Dreher, J.C., Schmidt, P.J., Kohn, P., Furman, D., Rubinow, D., Berman, K.F., 2007. Menstrual cycle phase modulates reward-related neural function in women. PNAS 104, 2465–2470.

Elliott, R., Friston, K.J., Dolan, R.J., 2000. Dissociable neural responses in human reward systems. J. Neurosci. 20, 6159–6165.

Elliott, R., Newman, J.L., Longe, O.A., William, Deakin, J.F., 2004. Instrumental responding for rewards is associated with enhanced neuronal response in subcortical reward systems. Neuroimage 21, 984–990.

Farde, L., Hall, H., Pauli, S., Halldin, C., 1995. Variability in D2-dopamine receptor density and affinity: a PET study with [11C]raclopride in man. Synapse 20, 200–208.

Febo, M., Ferris, C.F., Segarra, A.C., 2005. Estrogen influences cocaine-induced blood oxygen level-dependent signal changes in female rats. J. Neurosci. 25, 1132–1136.

Frye, C.A., Rhodes, M.E., Rosellini, R., Svare, B., 2002. The nucleus accumbens as a site of action for rewarding properties of testosterone and its 5α-reduced metabolites. Pharmacol. Biochem. Behav. 74, 119–127.

Gitelman, D.R., Penny, W.D., Ashburner, J., Friston, K.J., 2003. Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. Neuroimage 19, 200–207.

Goldstein, J.M., Seidman, L.J., Horton, N.J., Makris, N., Kennedy, D.N., Caviness Jr., V.S., Faraone, S.V., Tsuang, M.T., 2001. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. Cereb. Cortex 11, 490–497.

Grabenhorst, F., Rolls, E.T., Parris, B.A., 2008. From affective value to decision-making in the prefrontal cortex. Eur. J. Neurosci. 28, 1930–1939.

Gruber, O., Melcher, T., Diekhof, E.K., Karch, S., Falkai, P., Goschke, T., 2009. Brain mechanisms associated with background monitoring of the environment for potentially significant sensory events. Brain Cogn. 69, 559–564.

Gruber, O., Diekhof, E.K., Kirchenbauer, L., Goschke, T., 2010. A neural system for evaluating the behavioural relevance of salient events outside the current focus of attention. Brain Res. 1351, 212–221.

Haber, S.N., Knutson, B., 2010. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacol 35, 4–26.

Haltia, L.T., Rinne, J.O., Merisaari, H., Maguire, R.P., Savontaus, E., Helin, S., Någren, K., Kaasinen, V., 2007. Effects of intravenous glucose on dopaminergic function in the human brain in vivo. Synapse 61, 748–756.

Haltia, L.T., Rinne, J.O., Helin, S., Parkkola, R., Någren, K., Kaasinen, V., 2008. Effects of intravenous placebo with glucose expectation on human basal ganglia dopaminergic function. Synapse 62, 682–688.

Hedges, V.L., Staffend, N.A., Meisel, R.L., 2010. Neural mechanisms of reproduction in females as a predisposing factor for drug addiction. Front. Neuroendocrinol. 31, 217–231.

Hines, M., 2010. Sex-related variation in human behavior and the brain. TICS 14, 448–456.

Hines, M., 2011. Gender development and the human brain. Ann. Rev. Neurosci. 34, 69–88.

Hoeft, F., Watson, C.L., Kesler, S.R., Bettinger, K.E., Reiss, A.L., 2008. Gender differences in the mesocorticolimbic system during computer game-play. J. Psychiatry Res. 42, 253–258.

Hollerman, J.R., Tremblay, L., Schultz, W., 1998. Influence of reward expectation on behavior-related neuronal activity in primate striatum. J. Neurophysiol. 80, 947–963.

Hong, S., Hikosaka, O., 2008. The globus pallidus sends reward-related signals to the lateral habenula. Neuron 60, 720–729.

Ikemoto, S., 2010. Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory. Neurosci. Biobehav. Rev. 35, 129–150.

Kirsch, P., Schienle, A., Stark, R., Sammer, G., Blecker, C., Walter, B., Ott, U., Burkart, J., Vaitl, D., 2003. Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: an event-related fMRI study. Neuroimage 20, 1086–1095.

Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001a. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J. Neurosci. 21, RC159 〈http://www.jneurosci.org/content/21/16/RC159.long〉.

Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L., Hommer, D., 2001b. Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport 12, 3683–3687.

Knutson, B., Taylor, J., Kaufman, M., Peterson, R., Glover, G., 2005. Distributed neural representation of expected value. J. Neurosci. 25, 4806–4812.

Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog. Neurobiol. 72, 341–372.

Laakso, A., Vilkman, H., Bergman, J., Haaparanta, M., Solin, O., Syvälahti, E., Salokangas, R.K., Hietala, J., 2002. Sex differences in striatal presynaptic dopamine synthesis capacity in healthy subjects. Biol. Psychiatry 52, 759–763.

Lavalaye, J., Booij, J., Reneman, L., Habraken, J.B., van Royen, E.A., 2000. Effect of age and gender on dopamine transporter imaging with [123I]FP-CIT SPET in healthy volunteers. Eur. J. Nucl. Med. 27, 867–869.

Luo, S., Ainslie, G., Giragosian, L., Monterosso, J.R., 2009. Behavioral and neural evidence of incentive bias for immediate rewards relative to preference-matched delayed rewards. J. Neurosci. 29, 14820–14827.

Manoach, D.S., 2003. Prefrontal cortex dysfunction during working memory performance in schizophrenia: Reconciling discrepant findings. Schizophr. Res. 60, 285–298.

Mozley, L.H., Gur, R.C., Mozley, P.D., Gur, R.E., 2001. Striatal dopamine transporters and cognitive functioning in healthy men and women. Am. J. Psychiatry 158, 1492–1499.

Munro, C.A., McCaul, M.E., Wong, D.F., Oswald, L.M., Zhou, Y., Brasic, J., Kuwabara, H., Kumar, A., Alexander, M., Ye, W., Wand, G.S, 2006. Sex differences in striatal dopamine release in healthy adults. Biol. Psychiatry. 59, 966–974.

Munafò, M.R., Clark, T., Flint, J., 2005. Does measurement instrument moderate the association between the serotonin transporter gene and anxiety-related personality traits? A meta-analysis. Mol. Psychiatry 10, 415–419.

O'Doherty, J.P., 2004. Reward representations and reward-related learning in the human brain: insights from neuroimaging. Curr. Opin. Neurobiol. 14, 769–776.

Ossewaarde, L., van Wingen, G.A., Kooijman, S.C., Bäckström, T., Fernández, G., Hermans, E.J., 2010. Changes in functioning of mesolimbic incentive processing circuits during the premenstrual phase. Soc. Cogn. Aff. Neurosci. 6, 612–620.

Paus, T., 2010. Sex differences in the human brain: a developmental perspective. Prog. Brain Res. 186, 13–28.

Pohjalainen, T., Rinne, J.O., Någren, K., Syvälahti, E., Hietala, J., 1998. Sex differences in the striatal dopamine D2 receptor binding characteristics in vivo. Am. J. Psychiatry 155, 768–773.

Qureshi, I.A., Mehler, M.F., 2010. Genetic and epigenetic underpinnings of sex differences in the brain and in neurological and psychiatric disease susceptibility. Prog. Brain Res. 186, 77–95.

Rijpkema, M., Everaerd, D., van der Pol, C., Franke, B., Tendolkar, I., Fernández, G., 2012. Normal sexual dimorphism in the human basal ganglia. Hum. Brain Mapp. 33 (5), 1246–1252.

Rupp, H.A., James, T.W., Ketterson, E.D., Sengelaub, D.R., Janssen, E., Heiman, J.R., 2009. Neural activation in the orbitofrontal cortex in response to male faces increases during the follicular phase. Horm. Behav. 56, 66–72.

Samochowiec, J., Rybakowski, F., Czerski, P., Zakrzewska, M., Stepień, G., Pełka-Wysiecka, J., Horodnicki, J., Rybakowski, J.K., Hauser, J., 2001. Polymorphisms in the dopamine, serotonin, and norepinephrine transporter genes and their relationship to temperamental dimensions measured by the Temperament and Character Inventory in healthy volunteers. Neuropsychobiology 43, 248–253.

Schnider, A., Treyer, V., Buck, A., 2005. The human orbitofrontal cortex monitors outcomes even when no reward is at stake. Neuropsychologia 43, 316–323.

Schultz, W., 2000. Multiple reward signals in the brain. Nat. Rev. Neurosci. 1, 199–207.

van den Bos, W., McClure, S.M., Harris, L.T., Fiske, S.T., Cohen, J.D., 2007. Dissociating affective evaluation and social cognitive processes in the ventral medial prefrontal cortex. Cogn. Affect. Behav. Neurosci. 7, 337–346.

van Dyck, C.H., Seibyl, J.P., Malison, R.T., Laruelle, M., Wallace, E., Zoghbi, S.S., Zea-Ponce, Y., Baldwin, R.M., Charney, D.S., Hoffer, P.B., 1995. Age-related decline in striatal dopamine transporter binding with iodine-123-beta-CITSPECT. J. Nucl. Med. 36, 1175–1181.

Wacker, J., Dillon, D.G., Pizzagalli, D.A., 2009. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. Neuroimage 46, 327–337.

Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J., Evans, A.C., 1996. A unified statistical approach for determining significant signals in images of cerebral activation. Hum. Brain Mapp. 4, 58–73.

Zald, D.H., Cowan, R.L., Riccardi, P., Baldwin, R.M., Ansari, M.S., Li, R., Shelby, E.S., Smith, C.E., McHugo, M., Kessler, R.M., 2008. Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. J. Neurosci. 28, 14372–14378.

Zubieta, J.K., Ketter, T.A., Bueller, J.A., Xu, Y., Kilbourn, M.R., Young, E.A., Koeppe, R.A., 2003. Regulation of human affective responses by anterior cingulate and limbic mu-opioid neurotransmission. Arch. Gen. Psychiatry 60, 1145–1153.