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**Cigarette smoking reduces medication-
associated deficits in reward processing in
patients with schizophrenia**

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List of abbreviations

5-HT-2A receptor	5-hydroxytryptamine receptor 2A; a subtype of serotonin receptors
α 4 β 2 receptor	α 4 β 2 is a subtype of nicotinic receptors, Varenicline is a partial agonist
BDI	Beck Depression Inventory
BOLD	Blood Oxygen Level Dependent
BPRS	Brief Psychiatric Rating Scale
BS	Boredom Susceptibility
CLPZ	Chlorpromazine
CO	Control
CYP P450 1A2	Enzyme belonging to the cytochrome P450 system, involved in drug metabolism
D1 receptor	Dopamine receptor, D1 like family
D2 receptor	Dopamine receptor, D2 like family
D2/5-HT-2A	Ratio of binding affinity to dopamine (D2) receptors and binding affinity to serotonin (5-HT-2A) receptors of antipsychotics
DSM	Diagnostic and Statistical Manual of Mental Disorders
DIS	Disinhibition
ES	Experience Seeking
FBI	Federal Bureau of Investigation
fMRI	Functional magnetic resonance imaging
ICD	International Statistical Classification of Diseases and Related Health Problems

IGT	Iowa Gambling Test
LSD	Lysergic acid diethylamide; a semisynthetic psychedelic drug
ms	Millisecond
nAChR	nicotinic acetylcholin receptor
N	Number
PA	Patient
PANSS	Positive and Negative Syndrome Scale
PET	Positron Emission Tomography
RT	Reaction Time
RT delta	Reaction Time difference
SCID	Structured Clinical Interview for the DSM IV Axis I disorders
SD	Standard Deviation
SSS	Sensation Seeking Scale Form V
SPS	standard period of study
U	Unit
Vs	versus
WCST	Wisconsin Card Sorting Test

1. Introduction

1.1 Dopamine hypothesis

The hypothesis of a dysregulation of the mesolimbic-mesocortical dopamine-system is well established in the research of the neurobiological basis of schizophrenia (45). Studies analysing the mechanisms of action of antipsychotic drugs and later on molecular imaging studies pioneered this hypothesis. These studies (17, 50) substantiated the dopamine hypothesis of schizophrenia in proving that antipsychotics which are blocking D2 receptors can improve schizophrenic symptoms. More recent studies (1, 56) using radioligands like raclopride which bind to dopamine D2 receptors but are displaced by endogenous dopamine showed an increased raclopride displacement in schizophrenic patients in defined brain areas. Those findings indicate that the schizophrenic disorder is probably characterized by an excess of dopamine in the mesolimbic dopaminergic system including striatal brain areas. Dopaminergic dysfunction is still postulated as one of the major bases of schizophrenic psychopathology, although disturbances of other transmitter systems, like for example the glutamatergic one (31), have been shown to be relevant. The dysregulation of dopamine is thought to be characterized by regional differences in a way that there is a hyperdopaminergia in the mesolimbic system and a hypodopaminergia in more prefrontal regions. Along with this localization hypothesis, positive symptoms such as delusions and hallucinations are ascribed to a dopamine surplus in the mesolimbic system. Since D2 receptors are predominant in the striatum, they are especially affected. Negative symptoms like anhedonia and cognitive impairment are associated with a mesocortical dopamine shortage presumably leading to an upregulation of predominant D1 receptors (35).

Apart from its motor function, which becomes apparent in Parkinson's disease that is characterized by a dopamine deficiency, the human dopamine system is deeply involved in the reward system. The first evidence for this involvement came from animal studies. Studies using single cell conductions in non-human primates could substantiate the relation between expectancy and the receipt of a reward and dopaminergic response rates (26, 59, 78). Those studies showed that ascending dopaminergic neurons of the midbrain are important for motivational processes, the prediction of a reward and the signalling of prediction errors. Various flavoured sweets (cornflakes, grapes, apples) were presented as differently attractive rewards for the monkeys and brain activation was recorded during reward processing. Thereby it could be demonstrated that those midbrain neurons released dopamine in accordance to the receipt of a reward. The same effect was displayed if cues

were presented which were previously conditioned with reward (59, 72). When the predicted reward was higher or better than expected (positive prediction error) consistently higher firing rates of the dopaminergic neurons were detected. Likewise, a diminished dopamine release was found when the predicted reward was smaller or worse than expected (negative prediction error). However, the release of dopamine was only altered if the received reward was unequal to the predicted reward. If the predictive value of a cue was 100%, dopamine release remained unchanged. Alterations of dopaminergic firing rates can attribute value to extrinsic neutral stimuli that are thus provided with an attractive or aversive entity. The procedure of providing an extrinsic “cold” stimulus with an intrinsic attractive or aversive value is called “salience attribution”. Salience means that a stimulus is highlighted in a way that one would assign motivational behaviour to this stimulus rather than to another. The more salient a reward, the more eager a subject is supposed to be to receive it and hence to have a greater motivation for getting the reward. It is the mesolimbic dopamine system where such an attribution of salience is thought to mainly take place (79).

The findings of the animal studies could be replicated in imaging studies (66) of the human reward system. Meanwhile, a multitude of studies (12) support the link between alterations in dopamine release, reward related prediction errors and salience attribution. Heinz and Schlagenhauf (39) and Kapur (49) applied these findings to the investigation of schizophrenic psychopathology and elaborated the hypothesis of “aberrant salience attribution”. Based on previous hypotheses they suggested that stress induced or chaotic firing of dopaminergic neurons in the patients results in the attribution of salience to otherwise irrelevant stimuli. As Kapur stated, delusions can be interpreted as an effort of the schizophrenic patient to make sense out of the misled salience attribution and hallucinations might be a correlate of the experience of aberrant salience.

Since reward functions and schizophrenic psychopathology are linked through either involvement of the dopamine system, the reward system in schizophrenic patients has been the object of various surveys for many years. Already in the clinical routine, a relation between reward processing and the schizophrenic disorder can be observed. Many patients with schizophrenia are less approachable for everyday rewards like praise and are conspicuously hard to motivate e.g. for occupational therapy. Early on, several studies (40, 85) tried to influence the motivational deficit of schizophrenic patients with different methods, because this deficit of schizophrenic patients is, besides of the psychotic symptoms, a quite prominent characteristic in most patients. Various schemes of monetary

rewards were used, as well as praise or more detailed instructions to improve productivity or cognitive test results of schizophrenic patients and thereby also to influence the motivational deficit. But the findings of those studies were quite inconsistent. Some study results suggested an improvement through monetary rewards (83) whereas others found no effect on cognition or productivity by displaying rewards (70). However, it can still be deduced from those studies that there is a reward deficit in schizophrenic patients that is worth exploring furthermore.

1.2 Influential factors of reward deficits

There are several considerations regarding factors that could decrease or increase these reward deficits in schizophrenia. Psychopathology, smoking and antipsychotic medication primarily apply as possible influential factors on reward related brain activation. In a recent review, Ziaudeen and Murray (93) abstract the achievements of various behavioural and neuroimaging studies dealing with the correlations between reward related processes and schizophrenic psychopathology. One of those studies was a behavioural study from Roiser et al. (71) in which they used a Salience Attribution Test to explore disturbances of salience in schizophrenic patients. In this test, the probability of a reward was announced by a picture cue. This cue was varied in two dimensions (colour/shape) but only one dimension was task relevant and reinforced throughout the trial. During the test, subjects had to learn which probability was linked to which dimension. After the test, subjects had to indicate their estimated assignment of the dimensions to reinforcement. In this paradigm, Roiser et al. defined aberrant salience as the attribution of motivation to a neutral stimulus with no association to reinforcement. The authors were able to show that there is a correlation between aberrant salience attribution and delusional symptoms in medicated patients and also to negative symptoms in this reward learning paradigm. Also imaging studies detected corresponding relations. In another study from Juckel et al.(48), ten unmedicated patients with schizophrenia and ten healthy controls were scanned using fMRI during an incentive monetary delay task. During this task, the ventral striatal reward activity in the subjects was observed. Thereby they found a significant correlation between decreased ventro-striatal activity as a sign of diminished reward processing and the assessed severity of negative symptoms. On the basis of those and further study results Ziaudeen and Murray conclude in their review that there are reasonable arguments for a correlation between impaired reward processing in schizophrenic patients and severity of psychopathological symptoms.

Another possible factor influencing reward processing is antipsychotic medication. All currently licensed antipsychotic drugs block striatal D2 receptors in different degrees at clinical doses (27). This mechanism does not only entail the antipsychotic effects but has also an impact on the reward system itself. Different studies illuminated the impact of antipsychotic drugs on the reward system. The D2 receptor blocking effect of those drugs has been suggested to interfere with reward functions and in this way to cause secondary negative symptoms like decreased motivation and drive or anhedonia that mimic primary negative symptoms. In a survey of D'Aquila (20), rats which got a D2-like receptor antagonist (raclopride) showed a reduced duration of licking bouts of sucrose solution. Another survey of Kim et al. (53) using PET in schizophrenic patients and healthy controls, suggests that side effects of antipsychotics are linked with the blockage of D2 receptors in brain areas which are responsible for reward motivation and cognition. In an fMRI based study, Juckel et al. (47) could show that patients medicated with typical antipsychotics displayed a diminished activation in the ventral striatum after reward predicting stimuli compared to healthy controls or patients receiving atypical antipsychotic medication. This effect was ascribed to the prevailing characteristic of typical antipsychotics, the high D2 receptor blockage. Another interesting fMRI study concerning this theme was accomplished by Schlagenhauf et al. (76). Ten patients with schizophrenia were scanned first when receiving first generation antipsychotics and then after switching to the atypical antipsychotic olanzapine. Also ten healthy controls were scanned and compared to the patient group. All subjects had to do the same monetary incentive delay task and blood oxygen levels were measured during the anticipation of a reward. Only in the first scan, when patients received typical antipsychotics with a high D2 receptor antagonism, patients showed markedly reduced ventral striatal activation in comparison to healthy controls. This effect was correlated with negative symptoms. In the second scan, when patients were medicated with olanzapine, an atypical antipsychotic with a much lower affinity to D2 receptors, no significant difference to controls could be detected any more. Hence this could be a correlate of a D2 receptor blockage related appearance of negative symptoms.

Besides schizophrenic psychopathology and antipsychotic medication, smoking has been suggested as another important modulator of altered functioning of the dopaminergic reward system. Because nicotine as an addictive substance directly addresses the reward system, it appears reasonable to explore possible correlations between smoking and alterations in the reward system of schizophrenic patients. Compared to standard

population (25%), schizophrenic patients display an increased prevalence of smoking (60-90%) (22). Also in the clinical routine, a strikingly high nicotine consumption is observed in schizophrenic patients and there are several studies which dealt with possible explanations of the increased prevalence of smoking in schizophrenic patients. In patients with first episode psychosis, Zabala et al. (92) investigated the differences in cognitive functioning between smokers and non-smokers. Using a battery of neuropsychological tests, including the Stroop interference test and the Wisconsin Card Sorting Test, they could show that smokers with schizophrenia had better working memory and attention than comparable non-smokers and thus giving support to the hypothesis of smoking as a self medication in first episode schizophrenics. By these paths, it could be quite possible that smoking and nicotine could not only relieve cognitive but also motivational deficits related to reward functions. But till now there are no studies directly addressing this issue.

The current study was set up based on findings of an fMRI based study of our own group (87) Using a delayed incentive paradigm with monetary rewards, we investigated neural activation related to anticipation and receipt of rewards in patients with schizophrenia and healthy controls. All patients were treated with the same atypical antipsychotic, olanzapine. Like other imaging studies (48, 76) we could show a reward deficit in schizophrenic patients expressed in reduced activation of reward related brain areas compared to healthy controls. In our study it was shown that reaction time patterns in the monetary incentive delay task paralleled the BOLD signal patterns measured in reward processing brain areas. Likewise, in imaging experiments of healthy subjects faster reaction times and greater ventral striatal BOLD signal were both found with increasing rewards and interpreted as a correlate of motivation (29, 54, 65). Consequently, we suggest that reaction times in our monetary delay task can be seen as a predictor of fMRI activation in the ventral striatum. Hence it can be hypothesized that reaction times in this monetary incentive task alone could be a valid instrument to test reward related functions. If this turns out to be correct we would be in a position to suggest a new biomarker to investigate those functions independent of imaging methods and therefore simplify the testing procedures.

1.3 Primary and secondary endpoints

As primary endpoint we determined to demonstrate in a greater group of subjects, that the monetary incentive delay task as used within an fMRI framework (87) before, is a valid instrument to investigate correlates of an impaired reward system in schizophrenic patients. Like it was depicted in our previous study, we intended to replicate the findings of a diminished acceleration of reaction times between not and low rewarded trials as a potential expression of attenuated motivation in schizophrenic patients. Due to the fact that in the recent study we omitted the scanning part, we could test a greater number of cases than in the previous studies. Therefore we hoped to be able to investigate possible relationships of impaired reward related functions and psychopathology, smoking or medication i.e. possible modulators of the mesolimbic dopaminergic system in schizophrenia as secondary endpoints.

2. Methods

2.1 Subjects

49 patients with a diagnosis of schizophrenia according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) criteria were included in the study presented here. 22 additional patients with a diagnosis of schizoaffective disorder and three patients with delusional disorder were investigated within the same study framework but not included in the current analysis. We also had to exclude three patients because they abandoned the test before finishing it and two patients due to withdrawn consent after completing the test. In three patients, non-conformance with inclusion criteria was only detected after inclusion, i.e. epilepsy in one patient, drug-induced psychosis in another one and addiction to benzodiazepines in the third. One patient was excluded because he was found unable to perform properly in the test (for details see figure 1). Of the patients suffering from schizophrenia, 31 were diagnosed with paranoid schizophrenia (ICD-10, F20.0), 16 with undifferentiated schizophrenia (ICD-10, F20.3) and two with residual schizophrenia (ICD-10, F20.5). All patients were in-patients or patients of the day clinic of the Department of Psychiatry and Psychotherapy at the University of Ulm. Diagnoses were confirmed by one of two trained psychiatrists involved in the study. Symptoms were assessed using the Positive And Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). The included patients with schizophrenia were one-to-one matched to 49 controls in the following respects: gender, age and education. We had equal numbers of men and women in both groups. Between matched controls and patients there was a maximum difference in age of eight years in one case, but the average age difference was 2.2 years. Concerning education, we had five control subjects with an educational level one step higher than the matched patient (for details see table 1).

Exclusion criteria to our study were age under 18 or over 65 and any drug or alcohol addiction present or in the past five years. Control subjects were only included if they had no psychiatric or neurological history present or in the past. Additional psychiatric or neurological illnesses beyond schizophrenia were exclusion criteria for the patients. Control subjects were screened with a version of the Structured Clinical Interview of DSM IV axis I disorders (SCID I) for psychiatric disorders and patients underwent a semi-structured interview to confirm the diagnosis according to ICD-10 by one of the two trained psychiatrists involved in the study.

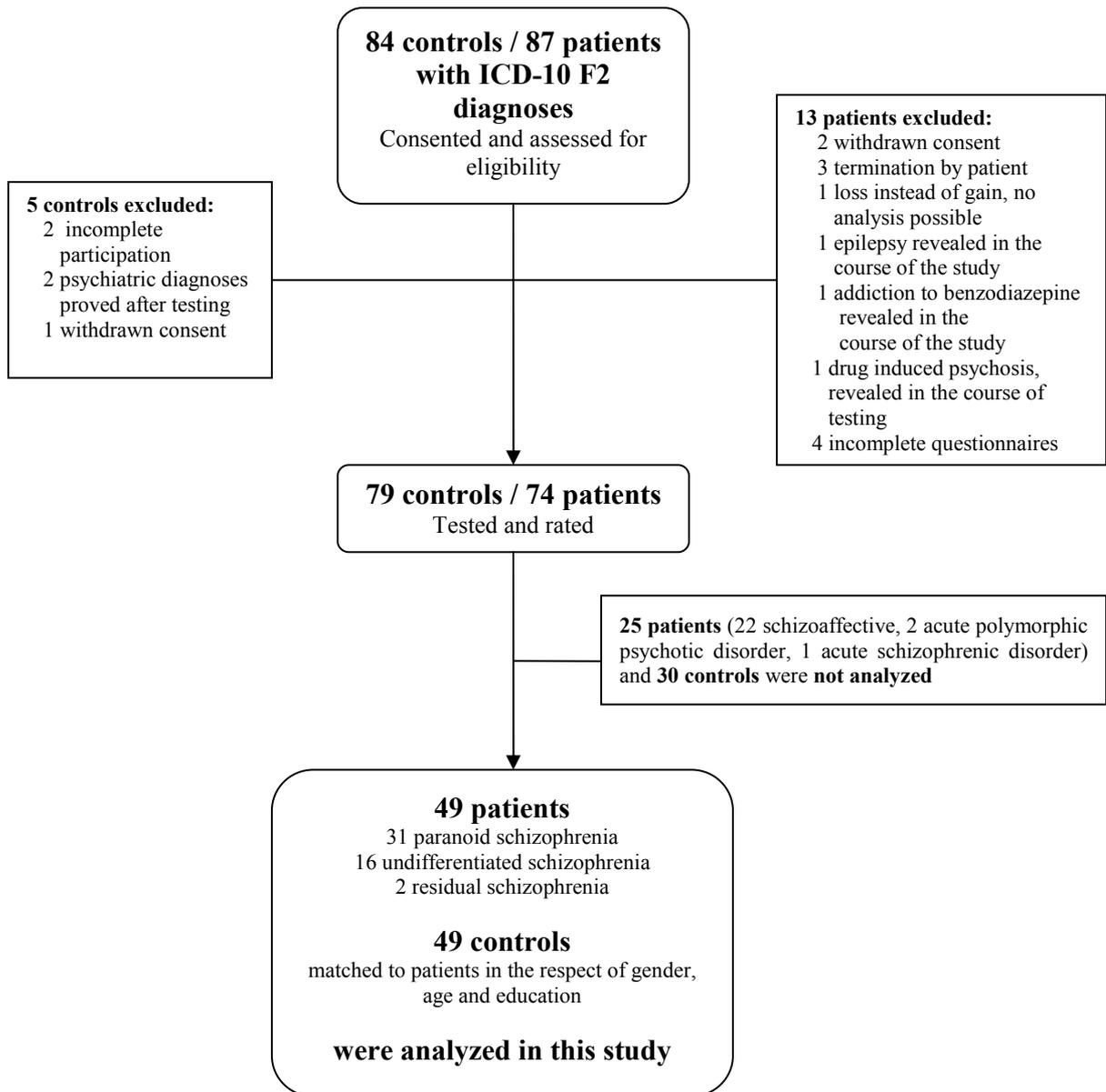


Figure 1: Flow diagram of initially recruited controls and patients. Numbers and reasons for exclusion in the course of the study.

No subject reported a history of alcohol or substance dependence present or in the past five years. Several participants denied any use of illegal drugs or abuse of medication like benzodiazepines (patients: n (number)=34, controls: n=33). Some reported occasional use of cannabis, less than ten times in their life (patients: n=2, controls: n=10) and some reported life-time use of cannabis more than ten times (patients: n=13, controls: n=6). Four of the patients and five of the controls reported having tried other illegal drugs (cocaine, LSD, ecstasy, speed, amphetamine, opium, heroin and appetite suppressant). Alcohol use was sampled in units (1U ~ ½ l of beer, ¼ l of wine or a double shot of hard liquor) per

time unit and divided in five subdivisions: (0) never or < 1U/month; (1) <1U/week; (2) 2-4U/week; (3) up to 7U/week; (4) >1U/day. The control group indicated a significantly higher consumption of alcohol ($t(96)=4.33$; $p= <0.001$). Actual numbers were: 7 controls/28 patients: never or < 1U/month; 16 controls/14 patients: <1U/week; 19 controls/2 patients: 2-4U/week; 7 controls/1 patient: up to 7U/week; 0 controls/4 patients: >1U/day.

Two of the patients and four of the controls were left-handed. 25 of the patients and 21 subjects in the control group smoked. Of these, two patients and two controls reported of smoking less than five cigarettes a day (for details see table 1).

Table 1: Demographic characteristics for included patients and controls

BDI (Beck Depression Inventar); SSS-V (Sensation Seeking Scale, Form V with the subscales of ES (experience seeking) BS (boredom susceptibility) DIS (disinhibition) TAS (thrill and adventure seeking))

* significant group differences in t-test (two-sided) at $p < 0.05$

education: In southern Germany, the basal education comprises 9 years of standard period of study (SPS). Pupils have the opportunity to achieve a higher education level with a secondary school certificate comprising of ten years of SPS. Pupils qualifying for university go through 13 years of SPS. There was one subject in the patients group with no graduation and 1 with a graduation in a school for children with learning disabilities. In the control group we had 1 subject without any graduation.

(+) in four of the control subjects and nine patients no reliable information about pack years was available

	Patients (PA) (n=49) ; n/n	Controls (CO) (n=49); n/n	
Male/ female	35/14	35/14	
Left-/ right-handed	2/47	4/45	
Smoker	25	21	
	<i>mean (SD)</i>	<i>mean (SD)</i>	<i>PA > CO t; p</i>
Pack years (+)	22.44 (17.0)	14.18 (13.9)	0.55; 0.14
Age (years)	35.06 (9.1)	35.02 (9.9)	0.021; 0.98
Education (years of SPS) #	10.72 (1.8)	10.75 (1.7)	-0.08; 0.94
Physical anhedonia	15.12 (6.7)	10.16 (6.4)	3.75; < 0.001*
Social anhedonia	13.78 (5.9)	8.0 (4.4)	5.50; < 0.001*
BDI	12.76 (8.8)	3.59 (3.9)	6.65; < 0.001 *
SSS-V (sum)	17.02 (5.7)	20.25 (6.9)	-2.53; 0.01 *
SSS-V (ES)	5.18 (1.9)	5.55 (1.9)	-0.96; 0.34
SSS-V (BS)	3.41 (1.9)	3.27 (1.8)	0.39; 0.70
SSS-V (DIS)	3.23 (2.1)	4.16 (2.4)	-2.04; 0.04
SSS-V (TAS)	5.20 (2.7)	7.27 (3.1)	-3.53; < 0.001*

All patients were medicated with atypical or typical antipsychotics or a combination of these. Haloperidol, amisulpride, risperidone, paliperidone, flupentixol, zuclopenthixol, clozapine, quetiapine, olanzapine, aripiprazole, ziprasidone, levomepromazine, chlorprothixene and melperone were each given to at least one of the patients. Six patients were additionally treated with an antidepressant (escitalopram, fluvoxamine or sertraline), four patients with an anticonvulsant (valproate or pregabalin) and ten were treated with a benzodiazepine (lorazepam with a maximum dose of 4 mg per day, clonazepam with a maximum dose of 3mg per day) as an add-on medication. None of the patients took lithium.

Antipsychotic medication was classified in two groups according to their pharmacological profile (9, 86): the one (high D2/5-HT-2A) comprised of drugs with a relatively high antagonism at D2 receptors as a main pharmacological principle (haloperidol [3], risperidone [8], amisulprid [10], paliperidone [4], flupentixol [1], zuclopenthixol [1]), the other (low D2/5-HT-2A) comprised of drugs with a relatively lower antagonism at D2 receptors and an accordingly low risk of extrapyramidal symptoms related to a high 5-HT-2A/D2 receptor affinity (drugs and numbers of patients receiving : clozapine (8), quetiapine [18], olanzapine [12], aripiprazole [7], ziprasidone [1], levomepromazine [1], chlorprothixen [1], melperone [1]). Numbers of patients treated with a certain drug are given in brackets [] and reflect also that several patients received more than one antipsychotic. Particularly quetiapine was frequently used as an add-on medication. As a partial agonist with a high affinity to D2-receptors and a low risk of extrapyramidal symptoms, aripiprazole was assigned to group 2. The dividing rule between ziprasidone and risperidone according to affinities reported in the literature (86) is a narrow one, but clinical experience allocates ziprasidone based on the lower incidence extrapyramidal side effects to the second group and risperidone to the first one. All patients taking at least one of the drugs out of the high D2/5-HT-2A group alone or in addition to medication from the low D2/5-HT-2A affinity group (2) were classified as patients treated with a regimen characterized by D2 antagonism, high D2/5-HT-2A group.

Chlorpromazine (CLPZ) equivalents were largely calculated according to the suggestions of Benkert and Hippus. (8) Thus, 100 mg of CLPZ were assumed to equal clozapine 50 mg, quetiapine 100 mg haloperidol 2 mg, levomepromazine 200 mg, risperidone 1 mg, amisulpride 100 mg, chlorprothixene 200 mg and flupentixol 2 mg. For paliperidone we calculated two times risperidone. The following equivalents were calculated according to the suggestions of Woods (89) with olanzapine 5 mg, aripiprazole 7.5 mg and ziprasidone

60 mg equaling 100 mg of CLPZ. According to the suggestions of Schneider and Niebling (77) Melperone 100 mg and Zuclopenthixol 20 mg were assumed to equal 100 mg CLPZ. For more detailed information about medication and assessment of schizophrenic psychopathology see table 2.

All participants, patients and controls, gave written informed consent after complete description of the study. The study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the ethics committee of the University of Ulm.

Table 2: Assessment of schizophrenic psychopathology in all patients

PANSS (Positive And Negative Syndrome Scale)

BPRS (Brief Psychiatric Rating Scale)

CLPZ: Chlorpromazine; antipsychotic medication was converted into CLPZ equivalents as described in the text

D2/5-HT-2A: quotient of receptor affinity of antipsychotics to dopamine D2 receptors and to serotonin 5-HT-2A receptors; haloperidol or risperidone e.g. have a relatively high quotient, olanzapine or clozapine have a relatively low quotient

	Patients (n=49); n/n
D2/5-HT-2A affinity relatively high / low	24/25
	<i>mean (SD)</i>
PANSS (sum)	30.45 (6.8)
PANSS positive	15.69 (4.4)
PANSS negative	16.18 (5.9)
BPRS (sum)	34.80 (7.9)
BPRS anergy	8.16 (2.9)
BPRS thought	7.65 (2.5)
Duration of illness (years since first diagnosed)	7.43 (7.4)
Duration of current episode (weeks of hospitalisation)	6.65 (11.1)
Medication (mg of CLPZ equivalents)	637.94 (338.5)

The splitting of the subjects in subgroups of smokers and non-smokers in the course of the analysis was related to some inequalities in the matching of the groups (smokers/non-smokers). In the patient group, significant differences between smokers and non-smokers occurred with respect to age, gender and the SSS-V disinhibition subscale (for details see table 3). However, as these characteristics were unrelated to reaction time differences in the whole group (see Results section), we considered the risk of a potential bias low.

Table 3: Patient sample characteristics for smokers vs. non-smokers

BDI (Beck Depression Inventar); SSS-V (Sensation Seeking Scale, Form V with the subscales of ES (experience seeking) BS (boredom susceptibility) DIS (disinhibition) TAS (thrill and adventure seeking))

** significant group differences in t-test (two-sided) at $p < 0.05$*

Education: In southern Germany, the basal education comprises 9 years of standard period of study (SPS). Pupils have the opportunity to achieve a higher education level with a secondary school certificate comprising of 10 years of SPS. Pupils qualifying for university go through 13 years of SPS. There was one subject in both groups with no graduation and one patient with a graduation from a school for children with learning disabilities.

	<i>Patient (PA)</i>		<i>PA Smoker > Non-smoker t;p</i>
	<i>Smoker (n=25); n/n</i>	<i>Non-smoker (n=24); n/n</i>	
Male/female	21/4	14/10	-2.02; 0.05 *
Left-/right-handed	1/24	1/23	
	<i>mean (SD)</i>	<i>mean (SD)</i>	<i>t; p</i>
Age (years)	38.28 (9.3)	31.71 (7.7)	-2.69; 0.01 *
Education (years of SPS) #	10.35 (1.7)	11.08 (1.8)	1.46; 0.16
Physical anhedonia	15.76 (6.6)	14.46 (6.9)	-0.67; 0.56
Social anhedonia	13.96 (5.7)	13.58 (6.3)	-0.22; 0.83
BDI	13.24 (9.6)	12.25 (8.2)	-0.39; 0.70
SSS-V sum	18.48 (4.6)	15.50 (6.4)	-1.86; 0.07
SSS-V (ES)	5.52 (2.0)	4.83 (1.8)	-1.27; 0.21
SSS-V (BS)	3.52 (1.9)	3.29 (2.0)	-0.42; 0.68
SSS-V (DIS)	3.84 (2.3)	2.58 (1.7)	-2.15; 0.04 *
SSS-V (TAS)	5.60 (2.4)	4.79 (3.1)	-1.03; 0.31

The group of smoking patients was on average 6.6 years older and included more males than the non-smoking patient group. In terms of characteristics of the schizophrenic disorder only one significant difference occurred. Duration of illness in smoking patients was on average 5.66 years longer compared to non-smoking patients (for details see table 4).

Table 4: Data of schizophrenia assessment for smoking and non-smoking patients

PANSS (Positive And Negative Syndrome Scale)

BPRS (Brief Psychiatric Rating Scale)

CLPZ: Chlorpromazine; antipsychotic medication was converted into CLPZ equivalents

D2/5-HT-2A: quotient of receptor affinity of antipsychotics to dopamine D2 receptors and to serotonin 5-HT-2A receptors; haloperidol or risperidone e.g. have a relatively high quotient, olanzapine or clozapine have a relatively low quotient

	<i>Patient (PA)</i>		<i>PA Smoker vs. Non-smoker t; p</i>
	<i>Smoker (n=25); n/n</i>	<i>Non-smoker (n=24); n/n</i>	
D2/5-HT-2A higher / lower	13/12	11/13	-0.42 ; 0.67
	<i>mean (SD)</i>	<i>mean (SD)</i>	<i>t; p</i>
PANSS (sum)	30.88 (5.2)	30.00 (8.2)	-0.45 ; 0.66
PANSS positive	16.56 (3.7)	14.79 (4.9)	-1.43 ; 0.16
PANSS negative	15.52 (4.1)	16.88 (6.5)	0.87 ; 0.39
BPRS- sum	34.48 (5.0)	35.13 (10.1)	0.28 ; 0.78
BPRS- anergy	7.72 (2.4)	8.63 (3.3)	1.11 ; 0.27
BPRS- thought	8.08 (2.6)	7.21 (2.4)	-1.22 ; 0.23
Illness (years)	10.20 (8.6)	4.54 (4.3)	-2.93 ; 0.01 *
Current episode (weeks after current hospitalisation)	3.97 (3.6)	9.47 (15.2)	1.72 ; 0.09
Medication (mg of CLPZ equivalents)	628.64 (350.5)	647.63 (332.8)	0.19 ; 0.85

In the control group significant differences between smokers and non-smokers only occurred in the SSS-V sum, SSS-V (ES) and SSS-V (BS).

Table 5: Sample characteristics in control subjects, separately for smokers / non-smokers

BDI (Beck Depression Inventar); SSS-V (Sensation Seeking Scale, Form V with the subscales of ES (experience seeking) BS (boredom susceptibility) DIS (disinhibition) TAS (thrill and adventure seeking))

** significant group differences in t-test (two-sided) at $p < 0.05$*

Education: In southern Germany, the basal education comprises 9 years of standard period of study (SPS). Pupils have the opportunity to achieve a higher education level with a secondary school certificate comprising of ten years of SPS. Pupils qualifying for university go through 13 years of SPS. There was 1 subject in the patients group with no graduation and one with a graduation in a school for children with learning disabilities. In the control group we had one subject without any graduation.

	<i>Control (CO)</i>		<i>CO Smoker vs. Non-smoker t; p</i>
	<i>Smoker (n=21); n/n</i>	<i>Non-smoker (n=28); n/n</i>	
Male/female	13/8	22/6	1.24 ; 0.21
Left-/right-handed	3/18	1/27	
	<i>mean (SD)</i>	<i>mean (SD)</i>	<i>t; p</i>
Age (years)	36.67 (10.4)	33.79 (9.4)	-1.00 ; 0.32
Education (years of SPS) #	10.55 (1.7)	11.89 (1.8)	0.98 ; 0.50
Physical anhedonia	9.14 (6.9)	10.93 (6.0)	0.95 ; 0.34
Social anhedonia	7.81 (3.6)	8.11 (5.0)	0.24 ; 0.82
BDI	4.38 (4.3)	3.00 (3.5)	-1.21 ; 0.22
SSS-V sum	22.53 (5.3)	18.54 (7.4)	-2.19 ; 0.04 *
SSS-V (ES)	6.33 (1.9)	4.96 (1.7)	-2.67 ; 0.01 *
SSS-V (BS)	3.86 (1.5)	2.82 (1.8)	-2.18 ; 0.04 *
SSS-V (DIS)	4.67 (2.2)	3.79 (2.5)	-1.30 ; 0.21
SSS-V (TAS)	7.67 (2.7)	6.96 (3.3)	-0.82 ; 0.43

2.2 Ratings and psychological testing

After the computer task, all subjects were asked to fill out several questionnaires. The German version of the Beck Depression Inventory (BDI) (37), Scales for Physical and Social Anhedonia (15, 19), the Sensation Seeking Scale (94), the Edinburgh Handedness Questionnaire (67) and the evaluation sheet were the same for all participants. We assessed all patients with the Positive and Negative Syndrome Scale (PANSS)(52) and the Brief Psychiatric Rating Scale (BPRS) (68). Those last two ratings were carried out by one of two trained psychiatrists involved in the study that also confirmed diagnostic criteria according to ICD-10. Controls were assessed with a version of SCID-I (88) to exclude psychiatric illness or substance abuse currently or in the past. Substance abuse was enquired in patients comparably.

2.2.1 Questionnaires

Beck Depression Inventory (BDI)

The BDI is a self assessment test to seize the severity of depressive symptoms (37). 21 clinical symptoms of depression are interrogated and rated from 0 to 3 by severity. In the assessment, sums between 0 and 63 are possible. Results below 11 points indicate the absence of depression whereas results over 18 are regarded as clinically relevant.

Scales for Physical and Social Anhedonia.

The two scales seize the inability to feel pleasure and ask for the personal inclination towards this in different situations (15, 19). It is a self assessment instrument that uses dichotomy questions (true/false). There are 50 questions concerning physical anhedonia and 40 questions concerning social anhedonia.

Sensation Seeking Scale (SSS-V)

Sensation seeking is defined by Zuckerman (94) as a personality characteristic which describes the search for novel or risky experiences. The level of individual arousal is maintained in avoiding or searching for such experiences. There are four subdivisions to the self-assessment Sensation Seeking Scale: TAS (thrill and adventure seeking), DIS (disinhibition – diversion through social contact), BS (boredom susceptibility) and ES (experience seeking).

Edinburgh Handedness Questionnaire

This self-assessment questionnaire developed by Oldfield (67) comprises of ten questions. In asking for preferences of left or right hand, foot or eye in activities of everyday life it determines the handedness. The intensity of lateralization is indicated by + (strong) or ++ (really strong) by the subject. Depending on a sum score, more or less strong laterality of handedness is assumed.

Positive And Negative Syndrome Scale (PANSS)

The PANSS is an external rating scale to seize the psychopathological symptoms of schizophrenic patients (52). 30 symptoms are rated on a scale between 1 (not existing) and 7 (fully developed). There is an assignment of symptoms to different sub-scales: positive symptoms, negative symptoms and common psychopathological symptoms. The PANNS judges the psychiatric state of the last 7 days and is based on the Brief Psychiatric Rating Scale (BPRS).

Brief Psychiatric Rating Scale (BPRS)

The basis is a clinical interview with 18 symptom complexes. It was developed by Overall (68) for hospitalised schizophrenic patients and rates symptoms such as fear, hostility and depression. On a scale with seven gradations (“not existing” to “extremely severe”) the severity of symptoms is assessed. The scale is considered suitable to evaluate the therapeutic progress.

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

The SCID-I is a semi- structured interview to test for the major symptoms and syndromes of the DSM-IV Axis I disorders (88). We used the SCID-I questionnaire primarily to exclude psychiatric illnesses in the control group. In a self assessment subjects first had to answer 12 screening questions regarding the most common psychiatric disorders and were subsequently asked for other symptoms as suggested in the interview guidelines.

Evaluation

Every subject was asked to rate the comprehensibility of the instructions and the legibility of the symbols presented in the reward task with yes or no. They were also asked whether they found the experiment too long/exhausting, whether they had problems concentrating and if so to explain the reason in an open question. Additionally, they were asked to

indicate whether they concentrated on the symbols announcing the height of a reward attentively or whether just the button press was more important to them. Finally they had to rate on a scale from 1 to 6 their joy or disappointed about the gain or loss of 20 cent or 1\$.

2.3 Task

Subjects were presented with a validated paradigm (3), a monetary incentive task with a parametric variation of possible wins (1\$, 20¢, no reward). All subjects were initially informed that after the experiment, 1\$ would be disbursed as 50 eurocents and 20¢ as 10 eurocents, no reward was no reward in either currency. Before the actual task, all subjects underwent one training session with the same set-up as the two experimental sessions. Each of the sessions consisted of 60 trials (5750 ms each; 10 no-reward-trials, 25 trials with potential gain of 1\$ and 25 trials with potential gain of 20¢). Each trial started with one of three symbols (cue, 750 ms) indicating the possible amount of money to win. After an expectation period (delay, 3000 ms), subjects had to react correctly with a left or right button press to one of two symbols (a square or a triangle; target) within a fixed interval of 1000 ms with the index or middle finger of their dominant (left or right) hand. Subjects were informed of this fact, i.e. that they did not need to react faster than that and that their chances to win were independent of their reaction times. In reacting correctly they preserved themselves a 60% chance to win the announced amount of money (1\$ or 20¢: reward trial). Therefore it follows that in 40% of the trials subjects were not rewarded despite pressing the correct button (omission trial). Incorrect button presses resulted in a feedback of zero Dollars at any rate. Reward and omission trials as well as the three trial types (1\$, 20¢, no reward) appeared in a random order. In the control trials (no reward) no money was announced, subjects were asked to press the right button nevertheless but they could not win any money. To make sure that all trials included a button press of any kind, subjects were informed that they would lose 1\$ if no button press occurred, and indeed, 1\$ was subtracted, if no button press occurred. Feedback (outcome, 1500 ms) followed the target's disappearance and notified subjects the amount of money they won in the trial. The monetary reward was shown to the subjects in dollars and cents as a sort of play money. Reaction times and errors were registered. Median reaction times were calculated across trials for each single subject, means were calculated to average over subjects (for details see figure 2). Only trials with correct responses were included in the reaction time analysis. A maximum of 30 errors was tolerated if there were enough trials to be analyzed.

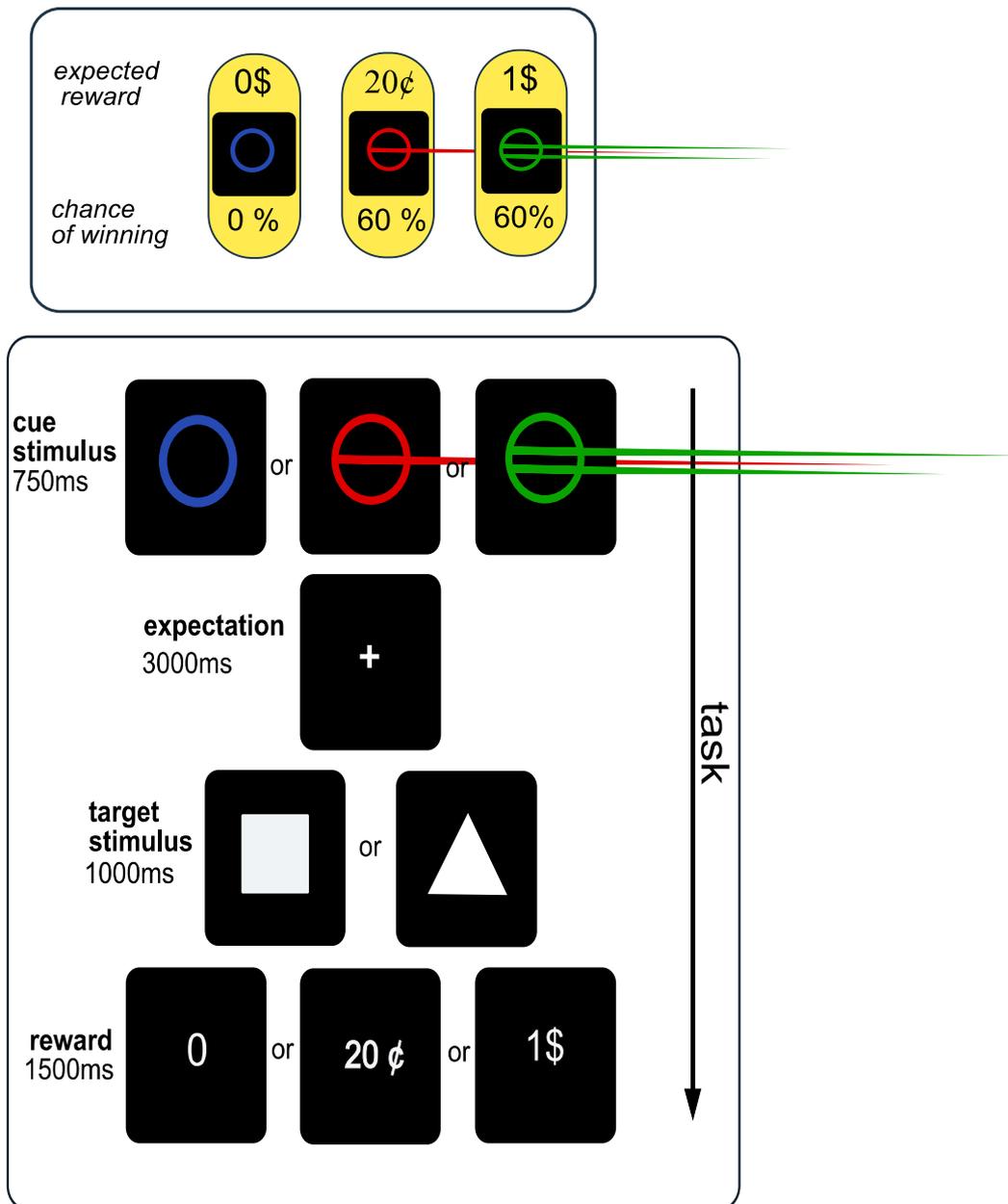


Figure 2: Monetary incentive delay task. Subjects were presented with different symbols indicating the chance for no/low/high monetary rewards for 750 ms. After an expectation period of 3000 ms, a target stimulus (square or triangle) occurred and subjects had to react correctly with either a left or a right button press. Correct button presses permitted a 60% chance to win the announced reward in the win trials. Incorrect button press lead to no reward win. No button press was related to the loss of 1\$.

2.4 Statistics

Statistics on sample characteristics and reaction time data were calculated using the software packages Microsoft EXCEL and Statistica 6.0. If not otherwise indicated, t-tests and correlations were considered significant at a p-level of 0.05, two tailed.

Means and standard deviations were calculated in the group of patients and controls as well as separately in smokers and non-smokers in each group for all questionnaire scores, sample characteristics and task related data (reaction times, reaction time differences, error-rates). To reveal significant interaction effects we used a 2x3 ANOVA with the factors group (schizophrenia/control) and condition (high reward/ low reward/ no reward). We compared reaction time differences (low – no reward) in patients and controls using a one-tailed t-test to directly test our a priori hypothesis of a reduced acceleration of reaction times from no to low reward trials in patients versus control subjects. A regression analysis with the acceleration data was applied out effects of age, sex, graduation, duration of illness or current episode. Another regression analysis was used to find correlations between D2-blockade, chlorpromazine equivalents, PANSS score and reaction time differences (low-no reward).

Two-tailed t-tests were calculated between controls and patients as well as between smokers and non-smokers for all questionnaire scores, sample characteristics and task related data (error-rates, reaction times, reaction time differences of low-no reward and of high-low reward trials) to reveal significant differences in our data. Correlations were calculated in patients and controls as well as in smokers and non-smokers between questionnaire scores and sample characteristics, between different questionnaire scores and between error rates and sample characteristics.

3. Results

3.1 Rating scales and clinical assessments

As expected for a clinical sample, patients had significantly higher results in the social and physical anhedonia scale and in the BDI as compared to healthy controls. In the SSS-V controls reached significantly higher results overall and in the disinhibition and the thrill and adventure seeking (TAS) subscales (for details see table 1). Significantly more patients (n=20) than controls (n=6) indicated problems with concentration during the test ($t(96) = -3.35$; $p=0.001$). In the evaluation questionnaire, subjects rated their joy or disappointment about receiving or failing to receive 1\$ or 20¢ in the monetary incentive task trials. Comparing healthy controls and patients there were no significant ($p<0.05$) differences detectable, but over all, controls rated to have experienced both, joy and disappointment, more intense than patients. There was only one significant difference in the control group between smokers and non-smokers detectable: Smoking controls rated their joy about receiving 20¢ as being higher than non-smoking controls (for details: table 6).

Table 6: Rated joy and disappointment about rewards for patients and controls:
On a scale from 1 to 6 subjects had to specify their joy or disappointment about receiving or missing 1\$ or 20cents. A rating of “1” indicated no joy or disappointment, a rating of “6” indicated marked joy or disappointment.

* significant group differences in a *t*-test (two-sided) at $p<0.05$

	<i>Patient (PA)</i>		<i>PA vs. non-smokers</i> <i>t ; p</i>	<i>Control (CO)</i>		<i>CO vs. non-smokers</i> <i>t ; p</i>
	<i>Smoker</i> <i>(n=25)</i> <i>mean;</i> <i>(SD)</i>	<i>Non-smoker</i> <i>(n=24)</i> <i>mean;</i> <i>(SD)</i>		<i>Smoker</i> <i>(n=21)</i> <i>mean;</i> <i>(SD)</i>	<i>Non-smoker</i> <i>(n=28)</i> <i>mean;</i> <i>(SD)</i>	
Joy about receiving 1 \$	3.48 (1.4)	3.58 (1.6)	0.24; 0.82	4.38 (1.4)	3.71 (1.3)	-1.72; 0.09 *
Joy about receiving 20cent	3.04 (1.1)	2.80 (1.1)	-0.78; 0.44	3.71 (1.1)	3.00 (1.1)	-2.29; 0.03 *
Disappointment about missed 1 \$	2.56 (1.9)	2.67 (1.6)	0.22; 0.83	3.29 (1.8)	3.04 (1.2)	-0.55; 0.58
Disappointment about missed 20cent	2.24 (1.2)	2.08 (1.4)	-0.42; 0.67	2.29 (1.2)	2.31 (1.2)	0.06; 0.95

Paralleling the differences found in the whole group between patients and controls, we found significant differences in the non-smoking group between controls and patients in the BDI, social anhedonia, physical anhedonia, the SSS-V overall, the SSS-V subscale disinhibition and the SSS-V subscale thrill and adventure seeking. Non-smoking controls had a higher consumption of alcohol ($t(50)=3.81$; $p=0.01$) than non-smoking patients and also significant differences were found in the use of illegal drugs ($t(50)=-0.88$; $p=0.004$). Other characteristics did not differ significantly ($p<0.05$).

Regarding correlational relationships between subject characteristics, in the following a threshold of $p<0.05$ applies for all correlations. For the whole patient and also for the control group we found a positive correlation between the SSS-V (ES: experience seeking) (controls: $r=0.54$; patients: $r=0.40$) or respectively the SSS-V sum (controls: $r=0.40$; patients: $r=0.34$) and the consumption of cannabis. Furthermore we found a positive correlation (controls: $r=0.42$; patients: $r=0.30$) between the BDI and the social anhedonia score in both groups.

Among the schizophrenia assessments, correlations were found between the PANSS negative score and the BPRS anergy score ($r=0.85$) as well as between the PANSS positive score and the BPRS thought score ($r=0.72$) as it was expected from the conceptualization of the scales.

3.2 Accuracy data

Overall error rates differed significantly ($t(96)=-6.36$; $p\leq 0.001$) between patients and controls and the effect was evident in all three trial types. Patients made on average 6.1% ($SD=4.9$) errors in the complete task, i.e. wrong or too late button presses, controls only 1.3% ($SD=1.7$) errors. Only in the patient group there was a correlation to be found between the number of errors and smoking status ($r=0.30$). Smoking patients displayed significantly higher overall error rates in the complete task than non-smoking patients ($t(47)=-2.16$; $p=0.04$). This was mainly due to a significantly higher number of errors in the not rewarded trials ($t(47)=-2.62$; $p=0.01$) in smoking patients compared to non-smoking patients (for details see table 7). Otherwise there were no correlations between errors and other sample characteristics. Comparing overall errors for non-smokers in the control and patient group significant differences were observed ($t(50)=-3.72$; $p<0.001$).

Table 7: Errors itemized for groups: percentage of errors in no-low-high rewarded trials and trial sum per subgroup. Error trials were not included in the analysis of reaction times.

* significant group differences in t-test (two-sided) at $p < 0.05$

	<i>Patient (PA)</i>		<i>PA smokers vs. PA non-smokers</i> <i>t; p</i>	<i>Control (CO)</i>		<i>CO smokers vs. CO non-smokers</i> <i>t; p</i>
	<i>Smoker</i> <i>(n=25)</i> <i>mean;(SD)</i>	<i>Non-smoker</i> <i>(n=24)</i> <i>mean;(SD)</i>		<i>Smoker</i> <i>(n=21)</i> <i>mean;(SD)</i>	<i>Non-smoker</i> <i>(n=28)</i> <i>mean;(SD)</i>	
Errors - No reward Trials	10% (8%)	5% (6%)	-2.62 ; 0.01*	2% (3%)	1% (3%)	-0.96 ; 0.32
Errors - Low reward Trials	7% (5%)	5% (5%)	-1.14 ; 0.26	2% (2%)	2% (3%)	0.06 ; 0.95
Errors - High reward Trials	7% (7%)	4% (4%)	-2.02 ; 0.052	1% (2%)	1% (1%)	-0.49 ; 0.61
Error-SUM	8% (5%)	5% (4%)	-2.16 ; 0.04*	2% (2%)	1% (2%)	-0.45 ; 0.66

3.3 Reaction time data

Comparing overall reaction times in patients and controls, we revealed faster overall reaction times in controls (high reward: 575ms / low reward: 584ms / no reward: 590ms) as compared to patients (high reward: 596ms / low reward: 610ms / no reward: 604ms) without reaching significance (for details see figure 4).

The 2x3 ANOVA with the factors ‘group’ (schizophrenia/controls) and ‘condition’ (high/low/no reward) did not reveal significant interaction effects ($F=1.77$, $p=0.17$). To directly test our hypothesis of a reduced acceleration of reaction times from no to low reward trials in patients versus control subjects, we compared reaction time differences (low – no reward) in patients and controls using a one-tailed t-test which revealed a significant effect ($t(96)=1.91$; $p=0.029$). While control subjects indeed showed the expected acceleration of -5.5 ms, patients even showed a deceleration of 6.1 ms (for details see table 8 and figure 4).

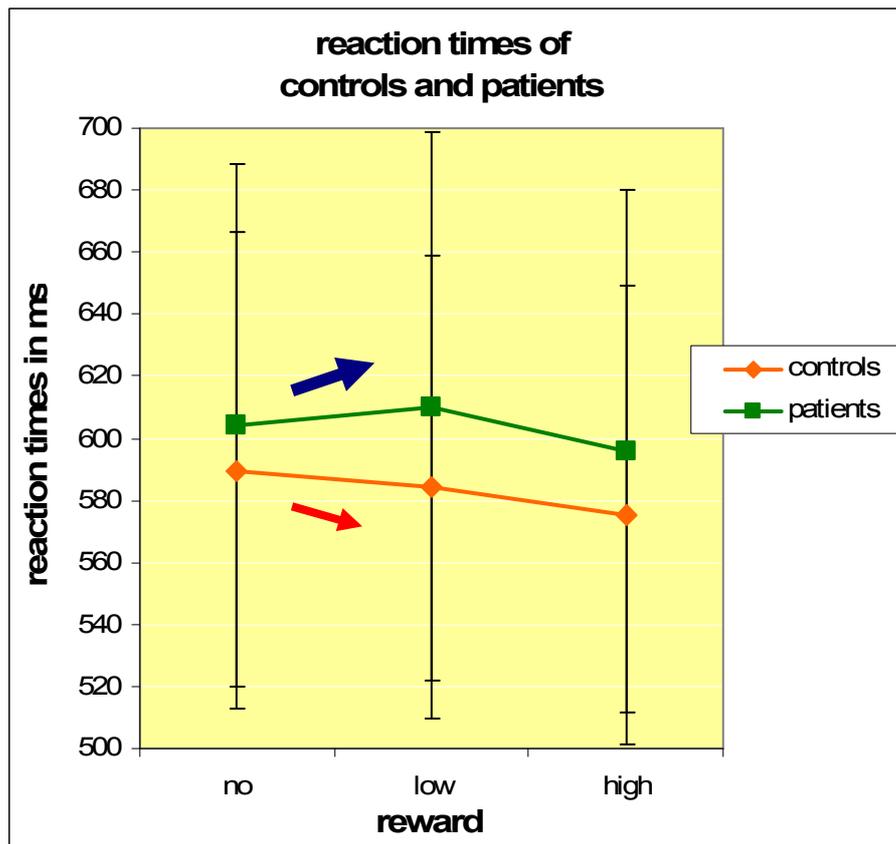


Figure 4: Reaction times and standard deviations for the three different reward levels in controls and patients irrespective of smoking status

Controls: $n=49$; patients (from the Department of Psychiatry and Psychotherapy at the University of Ulm): $n=49$.

A significant difference was found regarding acceleration/deceleration of reaction times with deceleration (blue arrow) in patients and acceleration (red arrow) in controls when comparing reaction time differences from no to low rewarded trials

Table 8: Reaction time differences (RT delta) for patient and control group between low and not rewarded trials on the one side and RT delta between high and low rewarded trials on the other side; negative RT deltas are accelerations of reaction times and positive RT deltas accordingly decelerations of reaction times from lower to higher rewards.

* significant group differences in t-test (one-sided) at $p<0.05$

	Patients ($n=49$) mean; (SD)	Controls ($n=49$) mean; (SD)	PA vs. CO t; p
Low- no reward (ms) RT delta (SD)	6,13 (28,7)	-5,5 (31,4)	-1.91; 0.03 *
High- low reward (ms) RT delta (SD)	-14.25 (32.3)	-9.15 (21.6)	0.92; 0.18

Table 9 : Reaction time differences (RT delta) for smokers and non-smokers of both groups between low and not rewarded trials on the one side and RT delta between high and low rewarded trails on the other side; negative RT deltas are accelerations of reaction times and positive RT deltas accordingly decelerations of reaction times from lower to higher rewards.

* significant group differences in t-test (two-sided) at $p < 0.05$
(ms): milliseconds; PA: patients; CO: controls

	Smokers		PA smokers vs. CO smokers <i>t; p</i>	Non-smokers		PA non-smokers vs. CO non-smokers <i>t; p</i>
	Patients (n=25) <i>mean; (SD)</i>	Controls (n=21) <i>mean; (SD)</i>		Patients (n=24) <i>mean; (SD)</i>	Controls (n=28) <i>mean; (SD)</i>	
Low- no reward RT delta (ms)	2.78 (26.2)	-0.07 (37.6)	0.29; 0.76	9.63 (31.2)	-9.57 (25.9)	2.39; 0.02
High- low reward RT delta (ms)	-12.24 (35.1)	-7.41 (23.9)	0.55; 0.60	-16.33 (29.7)	-0.46 (20.1)	-0.82; 0.40

A regression analysis ruled out effects of age ($r = -0.16$; $p = 0.26$), sex ($r = 0.23$; $p = 0.11$), graduation ($r = 0.0002$; $p = 1.0$) duration of illness ($r = -0.04$; $p = 0.81$) or current episode ($r = -0.05$; $p = 0.76$). However, neither PANSS ($r = 0.21$; $p = 0.15$) nor BPRS scores ($r = 0.21$; $p = 0.15$), nor status of medication ($r = 0.21$; $p = 0.15$) could help to explain the effect.

Because previous studies (22, 80, 90) have demonstrated influences of smoking status on reward behavior, we calculated the comparison of reaction time differences (low-no reward) separately on smokers and non-smokers. In comparison to non-smoking patients, smoking patients displayed slower overall reaction times without reaching significance (smoking patients: high reward: 601ms / low reward: 614ms / no reward: 611ms; non-smoking patients: high reward: 590ms / low reward: 607ms / no reward: 597ms). In the distinction between smoking and non-smoking controls there was no considerable difference in the overall reaction time (smoking controls: high reward: 577ms / low reward: 585ms / no reward: 585ms); (non-smoking controls: high reward: 573ms / low reward: 584ms / no reward: 593ms) (for details see figures 5 and 6).

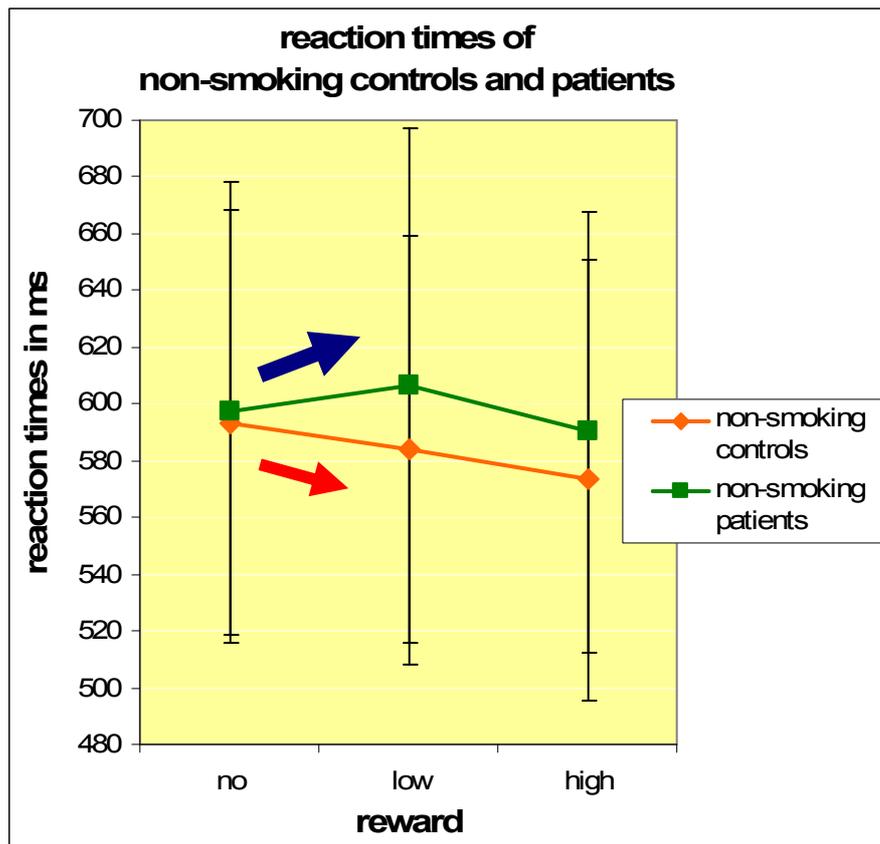


Figure 5: Reaction time data for different rewards in non –smoking controls and patients

Controls: $n=49$; patients (from the Department of Psychiatry and Psychotherapy at the University of Ulm): $n=49$.

Significant difference ($p<0.05$, two-tailed) regarding acceleration/deceleration of reaction times between no and low rewarded trials with deceleration (blue arrow) in patients and acceleration (red arrow) in controls when comparing reaction times from no to low rewarded trials.

Comparing patients and controls within the group of smokers, reaction time differences approximated zero (2.9ms in patients, -0.1ms in controls) without reaching significance ($t(44)=0.29$; $p=0.76$, two-tailed). Consequently, we found that the effect detected for the whole group was predominantly driven by the results in the non-smoking group, where we found a significantly greater acceleration ($t(50)=2.39$, $p=0.019$, two-tailed) in controls than in the patients. In fact, reaction times were decelerated from no to low rewards in patients (9.6 ms) but accelerated in controls (-9.6 ms), (for details see table 8 and figures 5 and 6).

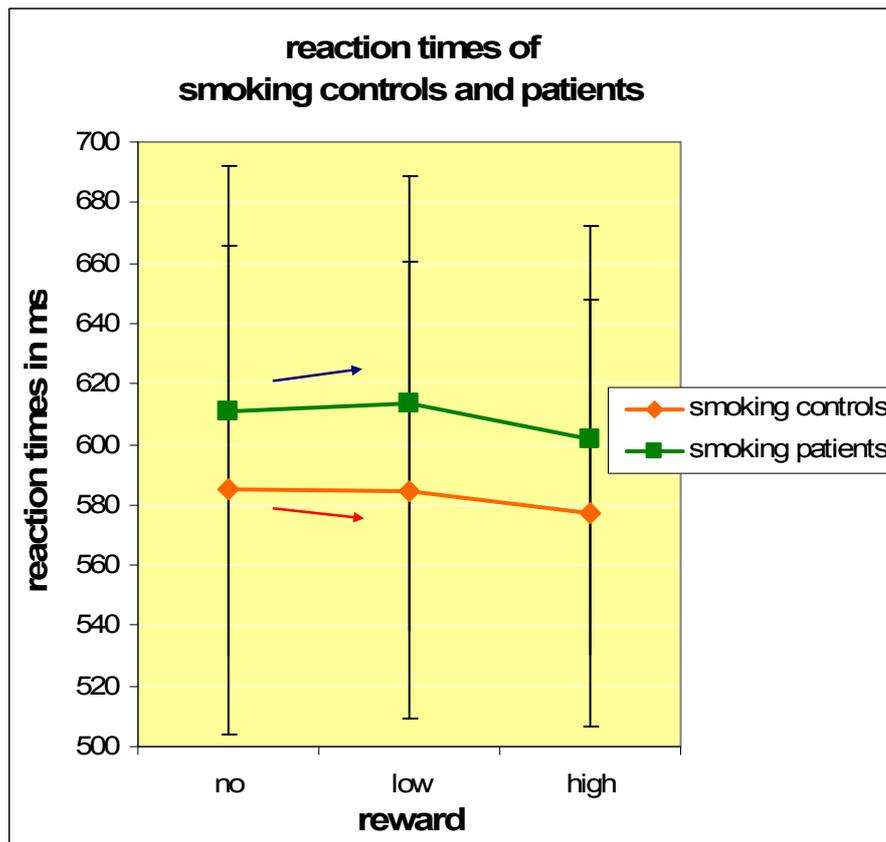


Figure 6: Reaction time data for different rewards in smoking controls and patients
Controls: n=49; patients (from the Department of Psychiatry and Psychotherapy at the University of Ulm): n=49.
No significant difference between reaction times with hardly any change in reaction times from no to low rewarded trials in both groups. Deceleration (blue arrow) and acceleration (red arrow)

A regression analysis ruled out effects of age ($r=-0.17$; $p=0.44$), sex ($r=0.18$; $p=0.36$) or education ($r=0.19$; $p=0.36$) in the non-smoking group. Exploring effects of medication and symptoms in non-smoking patients using regression analysis, we found a positive correlation of D2-blockade and reaction time differences ($r=0.41$; $p=0.045$), i.e. patients taking medication with a predominant D2 receptor blockade mechanism particularly tended to show this deceleration (see figure 7). There was a trend ($r=0.39$; $p=0.057$) towards a correlation with chlorpromazine equivalents (CLPZ) as well. D2 blockade and CLPZ were correlated ($r=0.49$; $p=0.014$) in this group. Likewise, there was a trend in the group of non-smoking patients towards positive correlations with the general psychopathology scale of the PANSS ($r=0.36$; $p=0.081$) and the PANSS negative scale ($r=0.35$; $p=0.097$), i.e. patients with more symptoms tended towards the deceleration (for details see figure 8).

Besides the correlation with reaction time differences, there was a correlation to be found between the receipt of D2 receptor blocking medication and reaction times in the low ($r=0.32$; $p=0.028$) and high rewarded trials ($r=0.35$; $p=0.016$). Patients taking D2 receptor blocking medication had significantly slower reaction times in the low ($t(47) = 2.28$; $p=0.03$) and also the high ($t(47)=2.38$; $p=0.01$) rewarded trials than the ones with little D2 receptor blocking medication.

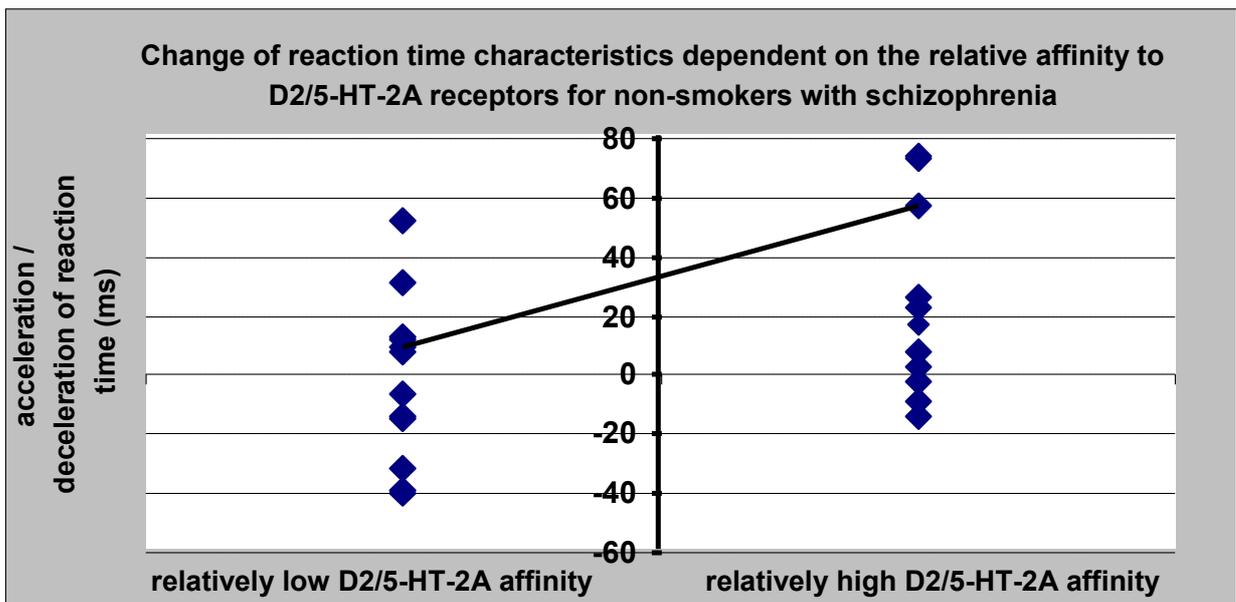


Figure 7: Reaction time differences (RT delta) between low and no reward trials in the group of non-smoking patients is correlated with D2/5-HT-2A affinity characteristics of received medication. Negative RT deltas are accelerations of reaction times from no to low rewarded trials and positive RT deltas are decelerations of reaction times from no to low rewarded trials, i.e. patients taking medication with a relatively high D2/5-HT-2A affinity display the most marked deceleration.

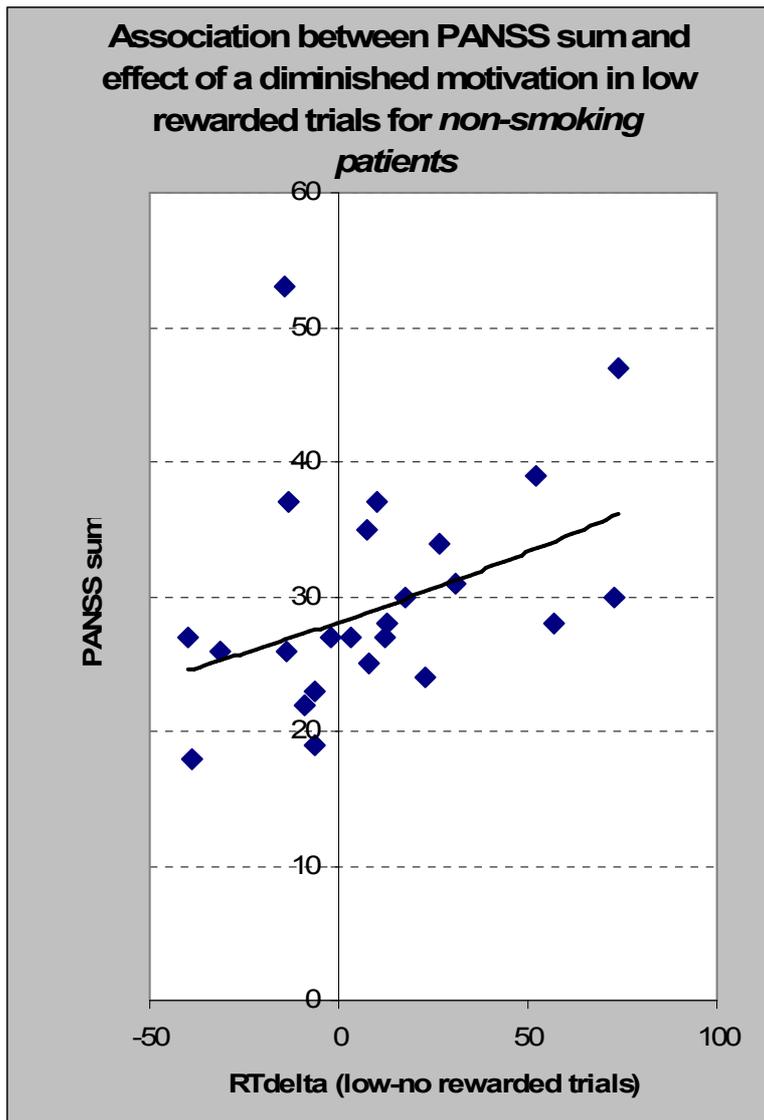


Figure 8: Trend towards correlation of the PANSS sum and reaction time differences (low-no rewarded trials) in non-smoking patients.

There was a trend towards a correlation between the PANSS (Positive and Negative Syndrome Scale) and reaction time data of not relative to low rewarded trials. Positive reaction time differences (RT delta) imply a motivational deficit i.e. patients showed slower reaction times in the low, compared to not rewarded trials. A higher score on the PANSS is associated with a diminished motivation in the low rewarded trials.

4. Discussion

4.1 Primary and secondary endpoints

Regarding our hypothesis of altered reward reactivity in schizophrenic patients using a monetary reward tasks with high and low rewards, we could verify our primary endpoint. We could replicate the finding from a small sample fMRI study of our group of a missing acceleration of reaction times in schizophrenic patients in low rewarded trials in a larger group of subjects. While high rewards compared to no rewards led to faster button presses in the patients as well as in the control group, low rewards compared to no rewards only lead to an acceleration of reaction times in the control group, but not in the patients. The fMRI study that was the background of the current study not only pointed towards a relation between reaction time data and brain activation, but also found that the missing accelerations in schizophrenic patients parallel the decreased activation of reward related brain areas of the mesolimbic dopaminergic system (87). As depicted in the introduction part, previous imaging studies (2, 3, 29, 48, 54, 65) formed the hypothesis that more motivating rewards lead to faster reaction times and concurrently increased fMRI activation in reward processing brain areas. Accordingly, less motivating stimuli were related to slower reaction times and weaker BOLD signals in the fMRI.

In this manner, reaction times can probably be seen as a correlate of motivation towards an incentive. In our data there was only a speed up of reaction time in schizophrenic patients between the low and high rewarded levels and not between the not and low rewarded levels. On the other hand, controls showed the expected acceleration of reaction times with low and high rewards. Due to the fact that reaction times can probably be seen as a correlate of motivation we can conclude that slower reaction times are an effect of reduced motivation. Hence it seems as if higher rewards were necessary to motivate schizophrenic patients compared to healthy controls. This lack of motivation could be attributed to negative symptoms like apathy and/ or to side effects of antipsychotic medication. The threshold which a reward has to overcome in schizophrenic patients may thus be higher than for healthy controls. Correspondingly, patients in our study only displayed accelerations of reaction times as a sign of enhanced motivation in the high rewarded trials. We concluded that the reaction time data in the monetary incentive delay task itself could be suited to picture reward deficits related to a dysfunction of the dopaminergic reward system in schizophrenic patients without more information from fMRI. Therefore we now take the chance to propose a possible new biomarker, which can capture psychopathology

related to a dysfunction of the reward system like anhedonia and lack of motivation in a reliable manner. Our suggested biomarker could allow examining reward deficits without the extensive set up of imaging studies. In this way persons could be tested, who were otherwise not amenable for imaging studies, like for example psychotic patients who are afraid of the fMRI tube. Another advantage lies in the higher feasibility of the data collection and therefore the possibility to test greater groups of subjects. Because of the relative nature of the reaction time differences, the measure seems reliable despite the overall slowing of reaction times as observed expectedly in our sample similar to previous studies (3, 87).

Moreover, replication of the findings in a larger group seemed reasonable to further investigate possible influencing factors of reward deficits, which was not possible because the number of subjects in the previous imaging study was low. In the first instance, the effect of a missing acceleration of reaction times in the low rewarded trials was not correlated to psychopathology or medication. However, when we split the groups in smokers and non-smokers it was apparent that particularly the findings in the non-smoking group drive the effect of the missing acceleration and here we found such correlations. To substantiate our hypothesis, we examined the reaction time differences between low and no reward trials of smokers and non-smokers in the patient group. Applicable to the hypothesis, smoking patients did not show the marked deceleration of reaction times in the low rewarded trials as non-smokers did. As faster reaction times are thought to be a correlate of motivation, it can be deduced that smoking patients may have less motivational deficits than non-smoking patients. Accordingly, they were more comparable to healthy controls in their reaction time patterns as shown in figures 5 and 6. Therefore, we concluded that smoking might affect deficits in reward-related and motivational behaviour in schizophrenic patients in a positive way. With regard to the previous study of Walter et al. (87) we were able to replicate a more specific deficit regarding reward processing, because we found the motivational deficit driven by the group of non-smoking patients. Furthermore, those non-smoking patients taking medication with a particularly high affinity to dopaminergic D2 relative to serotonergic 5-HT-2A receptors showed the effect of missing accelerations in the low rewarded trials particularly distinct. Furthermore, in non-smoking patients we found a trend with higher scores in the PANSS questionnaire with psychopathology correlating with the effect of missing accelerations.

4.2 A potential new biomarker to assess reward deficits

As depicted in the introduction part, negative symptoms such as lack of motivation and apathy are frequent observations in schizophrenic patients. Several studies tried to influence those deficits, but too little contemporary studies relating these to reward deficits are available and consistent in their findings. This conclusion was drawn in a recent Cochrane review about the efficiency of monetary incentives for schizophrenia by Michalczuk et al. (64). However, further research was recommended in the field of reward functioning, because monetary or other rewards could be used as positive reinforcement to enhance motivation in schizophrenic patients. Michalczuk et al. (64) suggested that monetary rewards could improve the patients motivation to complete specific tasks strengthening basic cognitive functions and thus lead to an overall greater quality of life. Especially negative symptoms, which are difficult to treat because they are also common side effects of typical antipsychotic drugs, could be affected in a positive way by the use of reinforcements. So far, reward deficits were quantified to some degree in behavioural testing (71) in exploring the effect of rewards on other biomarkers like cognitive performance in the WCST (Wisconsin Card Sorting Test) (40), or in measuring BOLD signals during reward tasks with the fMRI (47, 87). But with those methods reward deficits are quite elusive. Additionally, existing methods are rather indirect in their measurement of reward deficits like the WCST or are quite extensive as in the case of fMRI based methods. In contrast, measuring reaction times with our monetary incentive delay task is a far more direct way to measure motivational deficits.

4.3 Integrating the findings in the salience hypothesis of schizophrenia

The presently most common hypothesis about dopaminergic dysfunction in schizophrenia is the salience-hypothesis (49). In a disease free condition, the release of dopamine mediates the attribution of salience or behavioural relevance to incoming stimuli. In schizophrenic patients, the dopamine system is thought to release dopamine irrespective of the behavioural relevance of stimuli and even without relevant external or internal stimuli at all in the state of psychosis. It is a stimulus-independent firing of dopamine. This process is called “aberrant salience attribution” and means that behaviorally irrelevant stimuli are provided with meaning due to a dopaminergic firing in the state of psychosis. From the patients perspective, this means that suddenly previously unimportant external sensations or internal thoughts and ideas become salient. In an attempt to make sense out

of the flood of aberrant salience, patients develop delusions. This is why for example a patient with schizophrenia may think that an ordinary black car parking in the street in reality is an FBI car full of observing spies. Also, hallucinations are summarized as the experience of aberrant salience. Due to the aberrant dopamine firing, additional “noise” appears in the dopamine system. Therefore ordinary stimuli whose proper processing depends on dopamine releases like rewards or other behaviourally relevant stimuli have difficulties to be “heard” in this “noise” (49).

In our data, schizophrenic patients displayed faster reaction times for not rewarded trials than for low rewarded ones. Patients thus may have allocated more salience to the rather irrelevant stimulus of no reward than to the slightly more relevant stimulus of low reward. A similar effect of inappropriately strong responses in the ventral striatum to neutral cues in schizophrenic patients was detected by Jensen et al. (46) and interpreted in the context of aberrant salience attribution. They used a conditioning task with neutral and aversive stimuli, called Pavlovian learning. Compared to healthy controls, schizophrenic patients displayed an inappropriately stronger activation in the ventral striatum in response to neutral stimuli than to the aversive, much more salient ones. Patients also showed diminished striatal activation for errors of prediction in comparison to healthy controls. Jensen et al. interpreted this finding in the context of aberrant attribution of motivational salience to neutral stimuli.

In our data, schizophrenic patients displayed no acceleration of reaction times in the low reward trials but in the high reward trials they did. Thus it can be suggested as an interpretation that only the high rewards were attributed with enough salience to dominate the “noise” in the dopamine system of patients with schizophrenia. Less salient stimuli may have remained unheard in the aberrant dopaminergic firing.

4.4 Correlation between dopamine, motivation for a reward and reaction time

Our suggested biomarker relies on measuring reaction times in incentive delay tasks. As it was itemized previously, those reaction time data may be taken as a correlate of the subjects` motivation for receiving a reward. As it is known that reward functions are mediated by the neurotransmitter dopamine (66, 78), an impact of a dysregulated dopamine system in schizophrenic patients on reward related functions can be assumed. Subsequently, evaluating reaction time data in a reward task might render it possible to evaluate the functionality of the dopamine system. This supposition is also supported by

observations of imaging studies (87), which found the effect of altered reaction times in dependence of reward related brain activation correlating to dopaminergic function. In short form: because reaction times correlate with the motivation to receive a reward and the reward system is mediated through dopamine we suggest that it is possible to explore the dopaminergic reward system in analysing reaction time data. This chain of thought was considered to be valid vice versa as well. This is why we anticipated that patients who have a dysregulated dopamine system have altered reaction time data compared to controls.

4.5 Influential variables

4.5.1 Antipsychotic medication and motivational deficits

The suggested reward deficit in schizophrenic patients not only corresponds to clinical observations (33) but was also displayed in attenuated brain activations during reward processing in many fMRI studies besides our own. For example Juckel et al. (48) could demonstrate in a study with unmedicated schizophrenics that patients showed less ventral striatal activation during the presentation of reward predicting cues in a monetary delay task than healthy controls. The same effect appeared in another study of Juckel et al. (47) with a comparable design but this time with patients receiving typical antipsychotics. Once more, activation in the ventral striatum decreased in patients medicated with typical antipsychotics in comparison to healthy controls. Interestingly, this effect could not be demonstrated in patients receiving atypical antipsychotics. The reason why this effect of decreased activation was seen in unmedicated patients and also in those medicated with typical antipsychotics but not in those taking atypical ones, probably lies in the difference of their mechanism of action. Antipsychotic medication has been suggested to be able to ameliorate symptoms of psychosis by dampening the attribution of salience. Typical antipsychotic medication is thought to largely accomplish this by antagonising D2 receptors mainly in the striatum and is thereby probably able to prevent the overstimulation in a hyperdopaminergic state that has been suggested to underlie the symptomatology of acute psychosis (35). In our analyses, patients with a higher amount of D2 receptor blocking medication had slower reaction times in all trials in comparison to patients with less D2 receptor blocking. This is congruent with the hypothesis of an insufficient treatment under D2 receptor blocking medication when decreased motivation and reward related functioning are target symptoms (53). It is a core finding of

experiments with antipsychotic medication, that those medicaments attenuate the attribution of salience (49) as it is relevant not only in psychosis, but also physiologically in the context of rewards or other salient stimuli. On the one side this is why those drugs are effective against psychotic symptoms caused through aberrant, exaggerated salience attribution, but on the other side antipsychotics also dampen the attribution of salience which is necessary for everyday pleasurable drives and social interactions. Those secondary negative symptoms seen in the context of typical antipsychotics are supposed to be related to the degree of D2 antagonistic potency of those drugs (38). D2 receptors are mainly found in the striatum and D1 receptors mainly in the prefrontal cortex (35). As typical antipsychotic medication primarily antagonises D2 receptors, it is thought to take its primary effect in the striatum where it blocks the overstimulation of dopamine and thereby ameliorates psychotic symptoms (27). Atypical antipsychotic medication, however, is characterized by less blockade of D2 receptors but greater antagonism to serotonergic 5-HT-2A receptors (75). Through antagonistic features on the 5-HT-2A receptor, atypical antipsychotics increase dopamine levels in cortical regions. As it was mentioned in the introduction part, a shortage of dopamine dominant in the prefrontal regions of schizophrenic patients is hypothesized to explain negative symptoms. In increasing those prefrontal dopamine levels, atypical antipsychotic medication is suggested to be suited to alleviate dopaminergic hyperactivity in the ventral striatum because the inhibiting function of the prefrontal regions is restored. As it is known that the amount of blocked striatal D2 receptors is correlated with negative symptoms (38), it is understandable that atypical antipsychotics blocking less D2 receptors than typical ones are observed to relate to less secondary negative symptoms. Applicable to this is our finding in the group of non-smokers of a correlation between the intake of D2 receptor blocking drugs and the deceleration of reaction times in the low rewarded trials as an expression of a reward deficit (for details see figure 3). This phenomenon could be explained with a particularly strong decrease of reward-related functioning and motivation under the more D2 relative to 5HT2A antagonistic drugs.

4.5.2 Reward deficits and smoking

A particularly interesting finding of our study may be the finding that the reward deficit of schizophrenic patients could probably be affected by smoking. We could show that the reward deficit in patients depends on smoking status. Several studies (5, 90, 91) have demonstrated positive effects of smoking on cognition, attention or attenuation of drug induced side effects in schizophrenia. But to our knowledge, a direct connection between smoking and deficits related to reward, motivational functions and thus the functioning of the dopamine system has not been examined up to now. In a recent study of Hong et al. (43) about the effect of Varenicline (a partial agonist on nicotinic $\alpha 4\beta 2$ receptors, used for smoking cessation) on schizophrenia associated biomarkers, numerous surveys were outlined about the influence of smoking and nicotine on cognitive and neurobiological biomarkers associated with schizophrenia. Several studies demonstrated an improving effect of smoking on cognitive deficits and psychophysiological features associated with schizophrenia, like attention, working memory or sensory gating. Adler et al. (5) demonstrated in a group of 10 smoking schizophrenic patients and 10 healthy controls that auditory sensory gating is normalized in schizophrenic patients after the consumption of cigarettes. A baseline scan was performed after subjects were deprived from smoking overnight and a second one after subjects smoked as much as they wished. Changes in auditory sensory gating, which is impaired in schizophrenic patients were compared. Also Zabala et al. (91) demonstrated results indicating that smokers have better attention and working memory than non-smoking patients. In this study, they assessed 31 smokers and 30 non-smokers with first episode psychosis in various neuropsychological testings for cognitive functioning, for example the Stroop interference test. Smoking patients exhibited significantly better results in attention and working memory tests than the group of non-smoking patients. Further studies (6, 44, 82) directly addressed the effects of nicotine on psychophysiological and cognitive deficits. Already in 1996 Levin et al. (57) demonstrated an improvement of haloperidol induced impairments in memory performance and complex reaction time through the consumption of nicotine. They investigated the interplay of different doses of haloperidol and different doses of transdermal applied nicotine or placebo on memory function and reaction time in schizophrenic patients. As it was assumed, there was an impairment in delayed matching to sample choice accuracy and an increase in response time under haloperidol. In the trials with nicotine instead of placebo, an improvement of the haloperidol induced impairments of memory performances and complex reaction times was observed and this effect was correlated to the applied dose

of nicotine. Another survey concerning this effect comes from Dulude et al. (25). They measured the effect of nicotine gum versus placebo on mismatch negativity, a preattentive event-related potential index of auditory sensory memory, which is diminished in schizophrenic patients. During the testing, smoking schizophrenics and smoking controls were deprived from cigarette smoking for three hours and then assessed for the effect of acute nicotine consumption on mismatch negativity. Results indicate that nicotine can cause a normalization of impaired sensory memory function in schizophrenics. Using a nicotine nasal spray in a double-blind placebo controlled study, Smith et al. (82) found better results in spatial working memory and attention (assessed with the Connors' Continuous Performance Test) in schizophrenic patients after the intake of nicotine spray compared to placebo. Furthermore, regarding reward function, Yip et al. (90) tested cognitive function of smokers and non-smokers with schizophrenia and in comparison to healthy controls. They used the Wisconsin Card Sorting Task (WCST) to test cognitive flexibility and the Iowa Gambling Test (IGT) to test risk reward decision making. Although patients overall performed worse than controls in both tests, in the group of female schizophrenics, smokers had significantly better results than non-smokers. The results of those studies and the clinical finding of an increased smoking prevalence in schizophrenic patients led us to the consideration that an effect of smoking on our data is plausible as well. As the IGT affects reward processing systems, the finding of smoking induced improvements of the IGT supports our approach of splitting groups in the respect of smoking status.

Only in splitting the subjects in groups of smokers and non-smokers in our study, the alleviating effect of smoking on motivational deficits in schizophrenic patients became apparent. When we split both groups in smokers and non-smokers it was evident that smokers in the patient and control group had similar overall reaction time performances. The main difference between controls and patients was driven by the non-smoking group. A possible explanation to this effect is that nicotinic acetylcholin receptors (nAChR) which play an important role in cognition (63) are dysregulated (62) in schizophrenic patients. Stimulation of those receptors through nicotine is supposed to have various positive effects on cognitive performances by improving impulsivity and inhibitory dysfunctions(80). Thus, it may be possible that smoking induced activation of nicotinic acetylcholine receptors could also play a role for the improving effect on motivational deficits in our study.

While our data can add to the hypothesis that smoking may affect the functioning of the dopaminergic reward system in schizophrenia in a positive way, our sample of medicated patients does not allow for conclusions whether this effect is due to influences on the schizophrenic symptomatology itself or due to influences on side-effects of the medication for example via the release of dopamine upon the administration of nicotine (74). These two arguments have been formulated as subhypotheses of the self-medication hypothesis of smoking in schizophrenia before without findings clearly separating one from the other (84).

Although there was no difference in medication between smokers and non-smokers, the non-smokers in our study showed a greater reward deficit. Like mentioned above, Levin et al. and others (32, 57) showed the reversing of typical antipsychotic induced side effects through nicotine. In this line of arguments it could be assumed that smoking patients in our study could alleviate especially those reward deficits caused through secondary negative symptoms of D2 antagonising drugs. It is known that smoking can affect the metabolism of certain antipsychotic drugs (23). Nicotine induces the cytochrome P450 CYP 1A2 enzyme and in this way reduces the drug blood level of substrates such as antipsychotics (23). As aggravation of negative symptoms is a familiar side effect of antipsychotics with a high affinity to D2 receptors, mainly typical ones (53), one could ascribe the improved reward deficit in smokers to a smoking induced increase of metabolism of D2 receptor blocking drugs. However, we consider it highly unlikely that the effects are a mere result of a less effective medication regimen. On the contrary, smokers were included after a shorter period of inpatient treatment but did not differ from non-smokers regarding severity of symptoms or medication characteristics. Furthermore, a reduction of drug level by enzyme induction particularly applies for clozapine and olanzapine (60) and to a lesser extent for haloperidol (81). Amisulpride levels remain unchanged (10) and also levels of other antipsychotics like ziprasidone, aripiprazole or risperidone do not seem to be changed in a clinically relevant manner as they are metabolized via different pathways. However, clozapine and olanzapine, whose levels should be greatly affected by smoking, as antipsychotics with relatively low affinity to D2 receptors showed only minor effects on reaction times. Effects on reaction times were strongest under drugs with relatively high D2 affinity, predominantly risperidone and amisulpride that are less sensitive to smoking.

4.5.3 Reward deficits and Psychopathology

No matter if negative symptoms are caused secondarily by antipsychotic drugs or are integral to the schizophrenic disorder itself, they are assessed with the negative scale of the PANSS questionnaire. Since motivational deficits are conceptualized as part of the negative syndrome in schizophrenic patients and because motivational deficits are expressed in our collected reaction time data, a connection of reward deficits in the reaction time data and the PANSS score would be expectable. In our analyses, we found a trend towards a negative correlation between higher scores on the PANSS and overall slower reaction times in all trials. This effect could be ascribed to a probably worse condition of patients with more psychopathological symptoms at the time of testing. Interestingly, in the group of non-smoking patients there was a trend towards a positive correlation between a missing acceleration of reaction times in the low rewarded trials and the PANSS score (for details see figure 7). This effect was rather driven by high scores in the negative scale of the PANSS questionnaire than the positive scale. So, non-smoking patients with more psychopathological, especially negative symptoms displayed greater motivational deficits in the monetary incentive delay task than patients with fewer symptoms.

In this context, it is worth mentioning that smoking patients had slightly, but not significantly higher scores in the PANSS sum and PANSS positive scale, but had slightly, not significantly lower scores in the PANSS negative scale than non-smoking patients. Although those findings do by far not reach significance it could be speculated that the effect of smoking induced improvement of reward deficits and therefore less motivational impairments is expressed in lower scores on the PANSS negative scale. Similar results were reported in fMRI studies for example by Juckel et al. (48) or Schlagenhauf et al. (76) that found correlations between the reward deficit and psychopathology in schizophrenic patients. In those surveys, reward deficits were also correlated to negative symptoms.

4.6 Findings from the analysis of additional questionnaires

Analyzing the results of the SSS-V questionnaire, as a potential trait measure characterizing dopaminergic functioning we detected several parallels to other studies. We used this questionnaire because it was shown that it is a trait measure that correlates with reward related brain activation in dopaminergic brain areas (4). In our data, we found a relationship of SSS-V scores and smoking status. For smoking patients, we disclosed significantly higher scores on the disinhibition subscale of the SSS-V than for non-

smoking patients just as described by Derveaux et al. (21). In that study, Derveaux and his group compared 100 schizophrenic smokers and non-smokers in the respect of sensation seeking, impulsivity and anhedonia. Like it was seen in our data, significant differences between smokers and non-smokers appeared only in the disinhibition subscale of the sensation seeking scale. Derveaux et al. left the question open if “disinhibition is a preexisting driving force for smoking or the consequence of the pharmacological effect of nicotine on cognition and behaviour” (21) and suggested to further explore this finding in studies with former smokers. Liraud and Verdoux (58) suggested that higher accounts in sensation seeking could be associated with poorer medication adherence in patients with psychotic disorders and therefore be a possible source of confounds in our data. However, in our survey patients were under inpatient treatment at the time of testing and the intake of medication was carefully monitored.

Similarly to Kish et al. (55) who compared a group of patients with chronic schizophrenia with healthy controls, patients with alcohol dependence and general psychiatric patients, we found higher scores in the SSS-V sum for healthy controls than for patients with schizophrenia. In our data this effect was mainly driven by higher scores of controls in the thrill and adventure seeking part of the sensation seeking scale. An obvious explanation could be that volunteers for scientific experiments like ours tend to be people, who are eager to experience something new and possibly thrilling. Interestingly, smokers in the control group displayed also higher scores in sensation seeking than non-smokers in the control group, but this finding was more driven through higher scores in the subscales of “experience seeking” and “boredom susceptibility”. Altogether, sensation seeking scores were higher in smokers as demonstrated in several previous studies (18, 21, 51) although subscale results differed between patients and controls. In line with this are the findings of Gjedde et al.(30) who postulated an inverted u-shaped dependency of sensation seeking and dopamine occupancy respectively dopamine concentrations. Elevated scores in sensation seeking were associated with high dopamine occupancy and receptor density in the striatum.

Another finding in the analyses of our questionnaires concerns the evaluation sheet. Here, smoking controls indicated more joy but also greater disappointment about the received or missed rewards in comparison to non-smokers. This is interesting because smokers in the control group displayed more reward deficits, expressed in slower reaction times in the low rewarded trials than non-smokers. Apparently, although smoking controls subjectively

indicated stronger feelings regarding a reward, they objectively displayed greater motivational deficits than non-smoking controls. This effect could be explained by taking the different components of reward processing into account. Berridge and Kringelbach (13) postulated that reward processing is comprised of three components: liking, wanting and learning. While according to their suggestions, wanting (the motivation for a reward, including salience processes) and learning (acting on the experience of past rewards for making predictions, associations and representations for future rewards) are primarily dopaminergic, liking as the hedonic experience of a reward is mediated through the opioid and cannabinoid system. For our data this could signify, that the evaluated joy of an expected reward is probably rather part of the “liking” component of reward processing and the motivation assessed by measuring reaction times is probably more related to of the “wanting” component. As “liking” and “wanting” of reward processing are mediated through different transmitter systems, it could be assumed that negative effects of smoking rather relate to the “wanting” component of reward processing. The discovered reward deficit of smoking controls as part of the dopaminergic “wanting” component could therefore be separate from the evaluated joy or “liking” about an announced reward because the “liking” of a reward is rather related to the opioid / cannabinoid system which is not primarily affected by nicotine.

Comparing patients and controls, patients indicated generally less emotions than the control group, but among the patient group there was no significant difference to be detected between smokers and non-smokers. Particularly, in the low rewards there was no difference in the evaluated joy and disappointment and therefore it can be said that the motivational deficit we displayed in comparing reaction time differences is an effect which is independent of the subjective attitudes assessed by the questionnaires. Although our questionnaire results were not suited to capture the deficit assessed by the reaction times, better phrasing, directly asking for the subjects’ motivation to win, could yield different results.

4.7 Reaction time data of healthy smokers

Upon analyzing reaction time data and their modification through smoking in patients we made an astonishing observation in the reaction time data of smoking controls. It seems as if smoking has, besides of its positive effects on the reward processing in patients with schizophrenia, a rather negative effect for healthy controls. Although differences were not significant, it seemed as if in our data healthy smokers showed less acceleration between no and low rewarded trials than non-smoking controls. Their reaction time patterns rather resembled smoking patients with schizophrenia than non-smoking controls. However, this finding is in line with several previous allusions to negative effects of smoking on the vegetative reactivity in non-psychiatric populations. For example Diekhof et al. (24) in their review present studies demonstrating a decreased response to nondrug rewards in healthy smokers. Furthermore, a most recent fMRI based study of Peters et al. (69) replicated the effect of a reduced response to rewards unrelated to nicotine, this time for adolescent smokers. On the other side, drug related cues like smoking related pictures are typically accompanied with higher responses in the reward processing brain areas (34).

4.8 Hypothesis about the correlation of smoking and dopamine

On first sight, the effects of smoking for controls and patients detected in our study seem contradictory. Like it was described before, reward deficits in smoking schizophrenic patients seemed to improve under the consumption of nicotine. On the other side, healthy smokers rather seemed to develop some kind of a reward deficit through smoking as revealed by our data. Regarding the conspicuous differences between smokers and non-smokers concerning reaction time data, the question occurs how smoking or nicotine could differentially affect the reward system in patients and controls. Allusions for possible explanations come from different studies. A histochemical study (41) showed that there are nicotinic acetylcholine receptors on dopaminergic nerve terminals in the striatum and that the application of nicotine is able to effectuate the release of dopamine. Further studies using microdialysis (73) recorded dopamine release in rat brain slices after the application of different substances including nicotine. They showed that the administration of nicotine increased basal or ambient dopamine levels independent of action potentials in the ventral striatum. According to those findings, nicotine is probably partially able to increase dopamine release in defined brain regions. Remarkably, those findings could also be replicated in humans using PET. For example Brody et al (14) in a PET based study measuring the binding potential of radiolabeled raclopride showed that smoking increases

the dopamine release in the ventral striatum. In this study, the dopamine release in twenty healthy smokers was recorded, after permitting one half of the subjects to smoke before the second scan and denying it to the other half. The first scan was a baseline scan after the infusion of raclopride. As raclopride binding potentials correlate inversely with the released dopamine (raclopride binds on dopaminergic receptors but is displaced by endogenous dopamine), it could be demonstrated that the ones who smoked in the second scan had a greater endogenous dopamine release in the left ventral caudate, nucleus accumbens and left ventral putamen in this scan. This was interpreted as a probably acute effect of the nicotine intake. Another study from Busto et al. (16) investigated changes in raclopride binding potential as well, but this time in a cohort of depressed smokers, non-smokers and matched healthy controls. In this study, raclopride binding potential in the ventral and dorsal striatum was measured at baseline and three hours after oral application of amphetamine in 18 patients with major depressive disorder (8 smokers, 10 non-smokers) and 20 healthy controls (9 smokers, 11 non-smokers) using a PET scan. After the application of amphetamine, the raclopride binding potential in all subjects decreased. The most interesting finding of this study was that depressed smokers showed a decreased baseline raclopride binding compared to non-smoking patients or healthy controls. Also control smokers demonstrated diminished raclopride binding potential at the baseline scan. This indicates that in smokers probably more D2 receptors are occupied by endogenous dopamine and could therefore not be occupied by raclopride. The basal endogenous dopamine release thus seems to be augmented by nicotine.

If smoking increases the release of dopamine in healthy and depressed smokers, like it was just itemized, the same mechanism can be expected for schizophrenic smokers. As mentioned before, it is known from previous investigations (38, 53) that the percentage of D2 receptors blocked by antipsychotic agents is thought to correlate with psychomotor slowing and the negative symptom of apathy. In line with this, non-smoking patients who were medicated with D2 blocking antipsychotics showed the greatest reward deficit in our study. The amount of available dopamine receptors in those patients might be too low to guarantee an adequate transmission of reward related cues under conditions of relatively low salience. This situation could have lead to the observed motivational deficits in the reward- related reaction time task. When it is assumed that nicotine in smoking patients increases dopamine levels in the mesolimbic brain areas, it could be possible that the hence elevated dopamine levels in smoking patients account for the displacement of some of the D2 blocking drugs. The greater percentage of thereby again available receptors

could be responsible for the improved reward function in smoking patients. By this mechanism it could be explained how smoking via increased amounts of basal dopamine in the striatum could help attenuating negative effects of the D2 antagonism of typical antipsychotics to an extent which is sufficient to ameliorate motivational deficits but does not cause delusional symptoms.

However, according to previous investigations, reward deficits and related fMRI activity was also detected in unmedicated patients (48). In these, a hyperdopaminergic state is assumed that probably leads to an excessive occupation of striatal dopaminergic receptors. Hence it could be concluded that not only decreased, but also increased dopaminergic receptor occupancy in the striatal area seems to be related to reward deficits. This line of arguments could help to explain why healthy smokers in our study displayed a reward deficit in comparison to non-smoking healthy controls, depicted in a decreased acceleration of reaction times in the low rewarded trials. It might be comprehensible to assume that smoking controls increased their dopamine level in mesolimbic brain areas through the effect of nicotine to an extent which is rather hampering the physiological processing of salient stimuli than facilitating it. The interpretation of a slightly dysfunctional reward processing in smokers is in line with findings of a propensity to greater reward discounting (42) and related striatal hypo-responsiveness (61). Thus, there is some evidence that both, too many occupied D2 receptors and not enough available D2 receptors in dopaminergic brain areas are correlated with reward deficits. We assume that non-smoking healthy controls displayed optimal reward functioning, expressed in a progressing acceleration of reaction times with increasing rewards. We would like to suggest that there is an optimal interval for reward functioning related to the amount of occupied dopamine receptors in the striatum (also see figure 8). Non-smoking controls probably range within this optimal interval, whereas in smoking controls the optimal occupancy rate may already be exceeded. In this light it could be possible that smoking patients with schizophrenia benefit from a smoking induced increase of basal striatal dopamine levels which could bring the function of their reward system up to an intermediate level, similar to that of healthy, smoking controls.

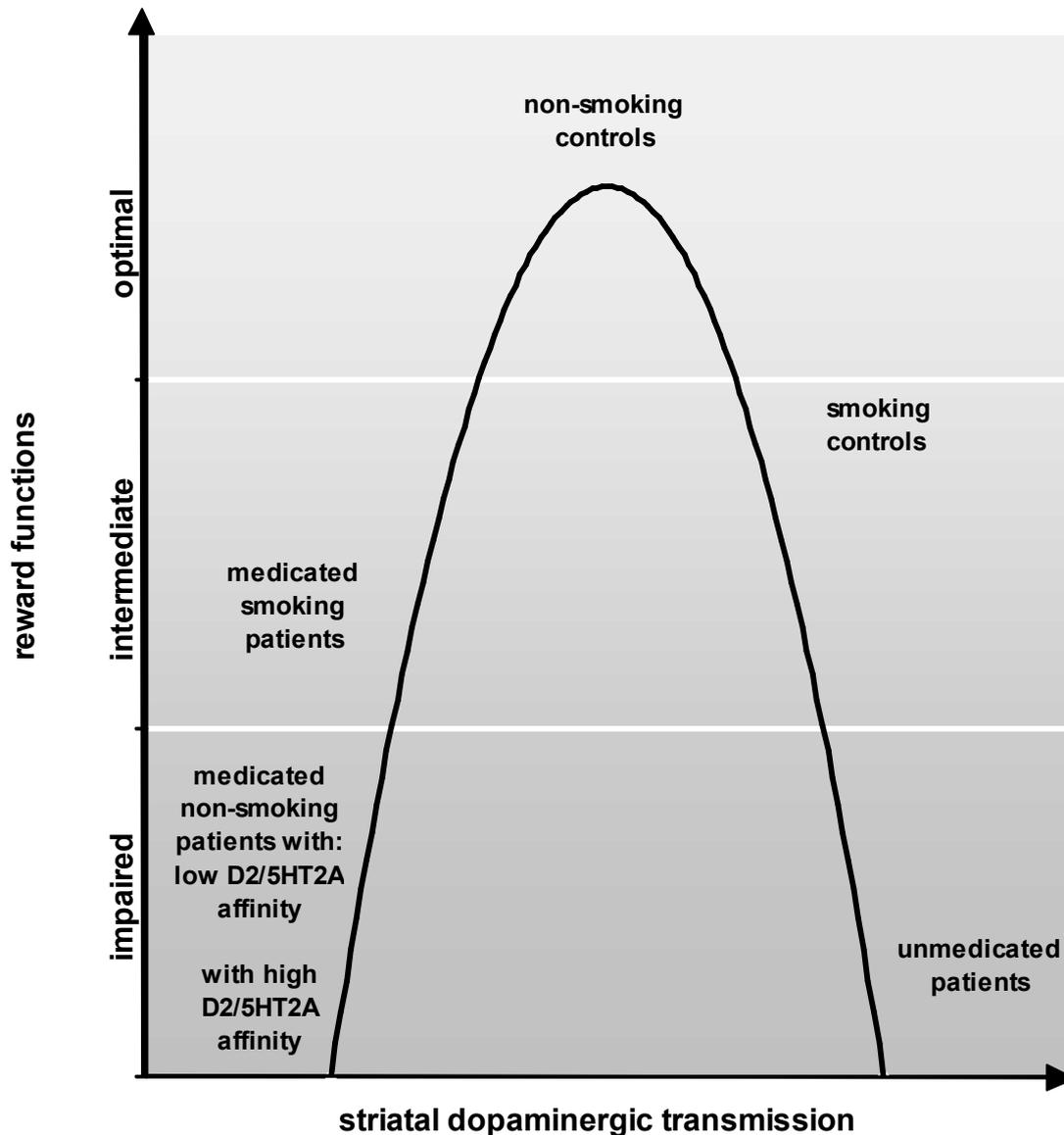


Figure 8: Suggested u-shaped model of a potential relationship of behavioural reward functions and the ventral striatal dopaminergic transmission. We suggest that there could be an optimal range of occupied dopamine receptors for ideal reward functioning. Both, too high occupancy of receptors with dopamine (like it is the case in unmedicated patients) and not enough occupancy (like it happens in non-smoking patients taking D2 receptor blocking medication) are related to decreased reward functioning. Smoking patients probably increase the amount of occupied receptors and therefore might thus improve their reward functioning. On the other side could the additional dopamine be accountable for the decreased reward function of smoking controls. Optimal reward function is suggested in non-smoking controls.

Our hypothesis of a u-shaped relation of cognitive functioning and activated dopamine receptors in relation to smoking is encouraged by a recent study of Hahn et al. (36). In this study, attention processing was assessed in 104 schizophrenic patients and matched controls with the attention network test and set in relation to their smoking status. The attention network test is a computer based, neuropsychological test to assess three

dimensions of attention processing: “orienting”, “alerting” and “executive control”. Through the combination of different cue stimuli and distractors the subject has to do a choice-reaction-task. Hahn et al. based their study on the assumption that nicotine enhances dopamine release and therefore increases the dopaminergic receptor binding. As attentional processes are commonly linked to the functioning of prefrontal regions, the hypothesis was built on the activation of D1 receptors and the prevailing hypodopaminergia in prefrontal regions. But nevertheless they found comparable results. Smoking patients could also improve attention deficits, whereas healthy smoking controls rather achieved worse results than non-smoking controls. Comparably to our hypothesis, Hahn et al. concluded that there might be a u-shaped dependency of attention processing and activated dopamine receptors. Unfortunately we could not find a correlation between a high dose of D2 blocking medication and an increased amount of smoking in the group of patients.

4.9 Problems related to splitting of the group

As a consequence of splitting the group in smokers and non-smokers by hindsight, some significant differences in group characteristics emerged and thus possible confounders were formed. However, it turned out that the group of smoking patients, which demonstrated less reward deficits than non-smoking patients, had collectively worse preconditions. Smoking patients had a longer duration of illness, were older and tended towards worse educational levels than non-smoking patients. Additionally, they made more errors during the trials, which could imply a worse accomplishment of the whole test. If these characteristics were to be held responsible for an effect, more deficits and thus worse performance in the test would be expectable. Instead, the group of smoking schizophrenic patients despite worse preconditions, displayed a motivational behaviour comparable to smoking healthy controls.

Another significant difference was observed in the gender distribution, with more males in the smoking patient group. There are some observations that female estradiol levels could be linked to a dampening of psychotic symptoms and to antipsychotic like effects (11). Hence it could be expected that females could benefit from those estradiol mediated antipsychotic effects and perform better than comparable males. In our group, however, the group of non-smokers, with more females, performed worse than the group of smoking patients with more males. Therefore it seems unlikely that those gender differences between both groups are a confounding factor biasing our results.

Further differences related to smoking status within the group of controls were limited to a trend towards higher consumption of illegal drugs for smoking controls. Maybe this phenomenon could be explained by referring to the results of the sensation seeking questionnaire. In the questionnaire, healthy smokers had higher scores than non-smoking ones, leading to the thought that smokers could be more approachable for new and thrilling things just like the use of illegal drugs. But there are also studies relating smoking and nicotine addiction to the consumption of illegal drugs (7, 28).

4.10 Limitations

Although our replication experiment in a much larger group of subjects allowed for drawing the hypothesized conclusions, an even larger sample size could have been more sensitive to effects. Thus more significant data could have probably been found in a study with a larger sample size.

Another point is that we did not measure blood levels for antipsychotics and could therefore not directly evaluate if or how smoking may have affected the drug metabolism in our patient group. However, previous investigations addressed the interaction of smoking and the metabolism of antipsychotic drugs and so we could make assumptions to possible influences of our data. Also interactions with other drugs are possible, given that most of the patients also received additional medication.

The differentiation between smokers and non smokers was done after finishing the study and could have produced confounding factors. However, as discussed above, the group differences generated in our data were not very likely to have bias our results.

5. Summary

Imaging studies have demonstrated that reward paradigms allow investigating the mesolimbic-mesocortical dopaminergic dysfunction in schizophrenia as the system is activated upon expectation and receipt of rewards. Altered activation of dopaminergic brain areas but also paralleling behavioural changes were found in previous studies. In a study of our own group, reward related acceleration of reaction times as found in healthy controls was only present upon high, but not low rewards in patients. However, the low number of participants of the previous imaging study made it difficult to generalize this finding and to link it to medication or psychopathology. To observe this, we used a mere behavioural approach and investigated 49 medicated patients with a diagnosis of schizophrenia and 49 matched healthy controls. Subjects were instructed to react with a certain button press to two different stimuli to have a 60% chance to win a previously announced amount of money (\$1.00 or \$0.20).

Along with greater anhedonia compared to controls, the prior finding of a missing acceleration of reaction times in patients with schizophrenia upon low rewards was replicated. The effect was pronounced in the non-smoking subgroup of patients in which we also found a positive correlation with the type of medication. Non-smoking patients who were taking medication like haloperidol, risperidone or amisulpride with a relatively greater D2/5-HT-2A (ratio of binding affinity to dopamine (D2) receptors and binding affinity to serotonin (5-HT-2A) receptors of antipsychotics) receptor affinity, displayed more motivational deficits than patients taking medication like olanzapine, clozapine or quetiapine with relative low D2/5-HT-2A receptor affinity. There was also a trend towards a correlation of the effect with the PANSS (Positive And Negative Syndrome Scale) scores. Conclusively, our study demonstrates that reaction time measures in a monetary reward task might constitute a feasible means to characterize dopaminergic dysfunction and its different dimensions regarding psychopathology but also medication in patients with schizophrenia. While previous behavioural studies on reward learning predominantly characterized prefrontal deficits in schizophrenia, we suggest the first behavioural measure to characterize ventral striatal dysfunction in line with imaging studies.

Furthermore we suggest that there could be an optimal range for ideal reward functioning which is dependent of occupied dopamine receptors. It seems as if this dependency could be u-shaped. Both, too high occupancy of receptors with dopamine, like it is seen in unmedicated patients and not enough occupancy, like it happens in non-smoking patients taking D2 receptor blocking medication, are related to decreased reward functioning.

Smoking patients are probably able to increase the amount of occupied receptors and therefore might thus improve their reward functioning. An almost optimal reward functioning could be assumed for non-smoking controls. On the other side smoking controls show a decrease in their reward function, possibly due to the additional dopamine level.

Along with the self-medication hypothesis of smoking in schizophrenia, our results suggest that nicotine consumption improves deficits in dopaminergic reward processing correlating with intake of D2-receptor-blocking medication. Therefore findings of our study are highly relevant for the clinical routine because schizophrenic patients display an increased prevalence of smoking (60-90%), compared to standard population (25%). Possible explanations for this have been researched and the amelioration of primary or secondary motivational deficits related to D2 receptor blocking medication, could further add to the self medication hypothesis of smoking. However there was no correlation between a high dose of D2 blocking medication and an increased amount of smoking in the group of patients to be found.

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Curriculum vitae removed for data protection