Neuropsychological and conditioned blocking performance in patients with schizophrenia: assessment of the contribution of neuroleptic dose, serum levels and dopamine D_2-receptor occupancy.

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ABSTRACT

Patients with schizophrenia show impairments of attention and neuropsychological performance, but the extent to which this is attributable to antipsychotic medication remains largely unexplored. We describe here the putative influence of the dose of antipsychotic medication (chlorpromazine equivalents, CPZ), the antipsychotic serum concentration of DA D2-blocking activity and the approximated central dopamine D2-receptor occupancy (DA D2-occupancy) on conditioned blocking (CB) measures of attention and performance on a neuropsychological battery in 108 patients with schizophrenia (compared with 62 healthy controls). Results: 1) Antipsychotic serum concentration and D2-occupancy were higher in patients with a paranoid vs. non-paranoid diagnosis, and in female vs. male patients (independent of symptom severity). 2) Controlling for D2-occupancy removed the difference between high CB in paranoid and impaired low CB in nonparanoid patients. 3) Similar partial correlations for antipsychotic drug dose and serum levels of the antipsychotic's DA D2 blocking activity with performance of the trail-making and picture completion tests (negative) and the block-design task (positive) show the functional importance of DA-related activity. 4) High estimates of central DA D2-occupancy related to impaired verbal fluency but were associated with improved recall of stories, especially in paranoid patients. This first study of its kind tentatively imputes a role for DA D2-related activity in left frontal (e.g. CB, verbal fluency) and temporal lobe functions (verbal recall) as well as in some non-verbal abilities mediated more in the right hemisphere in patients with schizophrenia.

Keywords: dopamine dopamine D_2 receptor neuroleptic antipsychotic dose serum level schizophrenia attention gender

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INTRODUCTION

Schizophrenia is an illness conventionally treated with drugs that primarily block the dopamine (DA) D2 receptor. Many patients with schizophrenia are impaired in performing cognitive tasks requiring selective attention (e.g. latent inhibition [LI] and conditioned blocking [CB]) and on neuropsychological tests of frontal or temporal lobe function (e.g. verbal fluency, card-sorting, logical memories: Straube and Oades, 1992).

Performance in healthy subjects is more easily disrupted by stimulation of DA activity with amphetamine on some of these tasks than on others (e.g. LI *vs*. CB, Gray *et al.,* 1992 vs. Gray *et al.,* 1997). But the impairments on these tasks in patients with schizophrenia are also associated with different features of the illness, such as the nature of the symptoms expressed and the duration of the illness. For

example, LI impairments are associated with florid symptoms and dissipate with illness duration (Gray *et al*., 1995): in contrast the CB impairment depends on nonparanoid features and is independent of the length of illness (e.g. Oades *et al*., 1996b; Bender *et al.* 2000). However, it is difficult to distinguish between the contribution of the illness to task performance from that due to the medication.

Most studies of the potential effects of antipsychotic drugs on the variables studied rely on converting the dose administered to a standard. The standard refers to the efficacy in reducing clinical symptoms and is usually expressed in terms of chlorpromazine equivalents (CPZ). However, the reliability of such data for antipsychotic drugs is compromised by four types of uncertainty. First, there is the uncertainty of compliance, that the medication was indeed consumed. Secondly, there are large pharmacokinetic fluctuations between individuals. The inter-individual bioavailability of the antipsychotic drug (i.e. the serum concentration) may vary more than 40-fold due to the high variation of resorption, metabolism and elimination. Thirdly, there are considerable pharmaco-dynamic variations between the effects of the various antipsychotic drugs (e.g. in the anti-psychotic effect as well as the disinhibition of prolactin release; Bagli *et al.,* 1999). Lastly, there is the likelihood that measures of clinical efficacy reflect antipsychotic actions on transmitters other than DA.

In this report we describe how these sources of error can be circumvented. We show how data on the doses of the antipsychotic drugs administered and on their bioavailability can be used to elucidate the contribution of DA D2-receptor antagonism to CB measures of selective attention abilities and neuropsychological tasks reflecting frontal, parietal and temporal lobe function. This report focuses on paranoid vs. nonparanoid schizophrenia as this distinction differentiates patients' attentional abilities measured by CB, and their likelihood to respond to neuroleptic medication.

The procedure starts with the determination of the serum concentrations of antipsychotic drugs in terms of their DA D2 receptor-blocking activity. This is achieved with an *in vitro* radioreceptor assay that quantifies the DA D2 receptor-blocking activity in serum in terms of haloperidol displacement from an aliquot of rat striatal tissue. The data from this assay correlate linearly with data obtained by chemical methods (e.g. high performance liquid chromatography: Rao, 1986). In one step this procedure identifies compliant patients and standardises between-patient and between-drug variability in terms of DA D2-binding activity.

Further, as most antipsychotic drugs are lipophilic and cross the blood brain barrier easily the data on antipsychotic drug dose can be used to estimate central DA D2 receptor-occupancy. This relationship is described in a number of positron emission tomographic studies (PET). We performed regression analyses on these PET data and report on the relationship to our data on the bioavailability of DA D2-binding activity in serum (neuroleptic units, NU) and the antipsychotic drug dose (CPZ). In this article we describe the relation of these three medication-related parameters (CPZ, NU and D2-occupancy) to our measures of psychological test performance.

Predictions of what this analysis should show in terms of the antipsychotic drugs' influence depend on two opposing views of how the DA D2-blocking activity should be interpreted. On the one hand high levels of antipsychotic drug binding activity could imply that more sites were occupied by the ligand as more sites were available than were occupied by DA: DA activity must be low. On the other hand for the DA D2-receptor high levels of binding sites can be built up to reflect high levels of DA release. In addition to this even low concentrations of antipsychotic drug will occupy synaptic DA D2-binding sites and interrupt the normal negative feedback circuit between synaptic levels of DA and DA release. This leads to an upregulation of the DA D2-receptor that reflects a lack of presynaptic control of DA release.

Our predictions are based on the latter of these two interpretations. The results may be

taken as a test between the two proposed mechanisms. First there is a widespread belief that DA D2-related binding may be increased in schizophrenia: this may be more marked in those exhibiting positive symptoms and underlie their responsiveness to neuroleptic treatment (Seeman, 1997; Straube and Oades, 1992, p. 604-5). Although direct evidence is sparse on this issue, we would predict increased D2-occupancy in patients with a diagnosis of paranoid schizophrenia (with positive symptoms) and less binding in those without these symptoms, reflecting hypodopaminergic function. Secondly, in animals, healthy humans and patients with schizophrenia CB varies with DA activity (Oades *et al.,* 1987; Oades *et al.,* 1996a, b). Thus it would be expected that either correlations of CB with D2-binding should be evident or controlling for the differences of D2-binding between subgroups of patients would abolish differences in CB reported for paranoid and nonparanoid patients. Thirdly, with regard to neuropsychological test performance we would predict a differential relationship for D2-occupancy with functions dependent on frontal vs. those dependent on temporal lobe function. This is based on the view that treatment with atypical neuroleptics contributes more to the improvement of cognitive function dependent on the frontal lobes (e.g. verbal fluency) than to improvement of memory dependent more on temporal lobe function (Meltzer & McGurk, 1999). The muscarinic binding potential of atypical neuroleptics may be the factor hindering an improvement of memory performance. Thus one could expect a relationship to appear between memory task performance and CPZ measures of antipsychotic drug administered, as this measure would reflect both dopaminergic *and* non-dopaminergic activity in the treatment.

METHODS

SUBJECTS

From 108 patients with schizophrenia, 107 were presented with a neuropsychology test battery. Of these 101 attempted the conditioned blocking (CB) task, and 62 learned the task well enough to allow a comparison with the performance of 62 healthy subjects, group-matched for age, years spent in education and socio-economic background (see Table 1).

Informed and signed consent was obtained from each patient, their responsible care-givers and the controls. The protocol was approved by the ethics committee of the University of Essen, Medical Faculty. Patients were recruited from the child, adolescent and adult psychiatry clinics and initial diagnosis was made by the senior psychiatrist. These patients were re-examined for entry to the study by two senior psychiatrists of the research group (S.B. and J.W.: DSM-IV, criteria A-E, American Psychiatric Association, 1994). Affective, schizoaffective and schizophreniform psychoses were excluded. Patients were additionally screened to exclude other major psychiatric or somatic illness, alcohol abuse in the last 5 years, and substance abuse other than nicotine. Schizophrenia subtypes were defined by DSM-IV criteria, whereby the undifferentiated type was regarded as a residual category that contrasts with the paranoid, disorganised and catatonic subtypes, (for clinical assessments and medication, see Table 1).

Symptoms were rated on the Positive and Negative Syndrome Scale (PANSS: Kay et al., 1992) and, as ideas-of-reference and thought disorder are under-represented in this scale, the relevant items 15-19 and 26-32 from the Scale for Assessment of Positive Symptoms (SAPS: Andreasen, 1982) were also scored. Clinical ratings included the scales for extrapyramidal symptoms (Simpson-Angus Scale, 1970), Abnormal Involuntary Movement Scale, AIMS, and the Barnes Akathisia Scale (1989).

The age of illness-onset was assessed by the therapist on interview with the patient and a relative: for some patients this was set as the date of the first psychiatric admission (range 8.9-45.8 years). Illness-duration was taken as the time elapsing between illness-onset and testing (range 0.02-20.1years). The duration of the current admission to the clinic ranged from 1 to 211 days. Antipsychotic drugs were administered to the patients according to the

Table 1

Demographic and Clinical Characteristics of the Subjects (Means ± standard deviation)

		Schizophrenics (acquired CB task) n = 62			Schizophrenics (did not acquire task) n = 39			Controls n = 62	
Age	(years)	30.4	(9.6)		37.1	(11.9)		32.5	(10.9)
Gender	(m/f)	44/18			21/18			33/29	
Socio-economic group[1]		4.6	(2.0)		4.4	(2.0)		4.9	(1.6)
Education	(years)	13.6	(3.9)		12.6	(3.3)		13.8	(3.0)
IQ	(short APM)	8.0	(2.7)		5.6#	(2.6)		9.9#	(1.9)
Hand	(Edinburgh)	16.8	(9.6)		18.7	(6.0)		18.9	(5.3)
Diagnosis									
Paranoid		41			29				
Disorganised		16			8				
Catatonic/residual		2/2			1/1				
Age of onset	(years)	23.2	(8.1)		23.3	(7.3)			
Duration of illness	(years)	7.2	(6.4)		13.4**	(8.8)			
Symptoms									
PANSS	Positive	15.5	(5.9)		17.6	(6.2)			
	Negative	18.1	(8.4)		19.5	(7.8)			
	General	36.0	(9.7)		38.1	(9.1)			
SAPS	Ideas of reference	3.0	(3.3)		3.5	(4.5)			
	Thought disorder	8.2	(7.3)		8.8	(5.6)			
EPS		3.0	(4.1)		4.8	(6.7)			
AIMS		7.9	(2.4)		8.2	(2.9)			
Antipsychotic dose (CPZ)[2]		617	(340)	(n=59)	732	(311)	(n=39)		
Biperidene	(mg/day)	4.2	(1.6)	(n= 9)	4.8	(1.8)	(n= 5)		

1. Scale 1-7, (Brauns et al., 1997): **2**. Two medication-free, 32 vs. 15 on 'typical', 19 vs. 18 on clozapine or olanzapine, and 9 vs. 6 on both typical and atypical neuroleptics.

# $p < 0.001$ ($t = +4.3$, between patient groups, $t = -4.6$ between subjects that acquired the CB task)

** $p < 0.003$ (with respect to the patient group that acquired the CB task)

AIMS, Abnormal involuntary movement scale; APM, Advanced progressive matrices; CPZ, chlorpromazine equivalents; EPS, Extrapyramidal symptoms; PANSS, Positive and negative syndrome scale; SAPS, Scale for the assessment of positive symptoms

clinical requirements and the dose was normalised to chlorpromazine equivalents (CPZ) according to Benkert and Hippius (1986), Rey et al. (1989), Schulz et al. (1989), Kane (1996) and correspondence with the firms supplying olanzapine and sertindole. Of 107 patients entering the study, two male patients were without medication at the time of testing, 49 (63% male) were administered typical antipsychotic drug medication, 43 (67% male) received atypical medication (clozapine and olanzapine), and 15 (47% male) had a combination of both types of drug. In terms of the diagnosis of paranoid (n=76) vs. nonparanoid (n=31) schizophrenia 40 vs. 9 received typical, 25 vs. 18 received atypical and 11 vs. 4 received both types of medication. Fourteen patients received

biperidene (mean 3.9 mg, range 2-8 mg; Table 1).

The 62 healthy subjects were recruited by advertisement and were paid for participation. The selection controlled for the socio-economic distribution and age among the patients: gender ratios were not significantly different (Table 1). The exclusion criteria for healthy subjects, based on a semi-structured interview were the same as described for the patients. In addition they reported no family history of psychotic illness, nor that they had previously consulted with a psychiatrist or psychologist.

The Conditioned Blocking (CB) Test of Selective Attention

CB refers to the delay in learning about the consequences of a stimulus-component (B in AB) when these consequences are already becoming associated with another component (A in AB). In other words, attending to and conditioning to the one component is said to be 'blocked' by attending to and conditioning to the other (Kamin, 1969). This 'blocking' is evident in healthy subjects in the delayed response to component B (with respect to that to A) when the components are presented separately at the end of the task in a test of learning. This 'blocking' is normal because as the learning criterion of response to AB is approached, responding becomes more automatic. With the presentation of a single component when testing for the learning that has occurred about each component, information processing must be switched back to a controlled conscious mode, as was evident at the start of conditioning.

The CB task was introduced as a computer game. A cursor could be moved with a joystick through a maze resembling the floor-plan of an apartment (see Fig. 1). Subjects could start from the left or right sides of the maze and were asked to find a goal in the other room with the cursor (i.e. 2 goal loci in mirror image positions). On reaching the goal the locus turned pale yellow and 30 points were awarded on counters below the maze. Every second beyond a latency of 8 sec was scored with -1 point per second. Such trials were scored as 'errors' for the calculation of the learning criterion. The inter-trial-interval was 2 sec. Skilled subjects learned to reach the goal in about 2.4 sec.

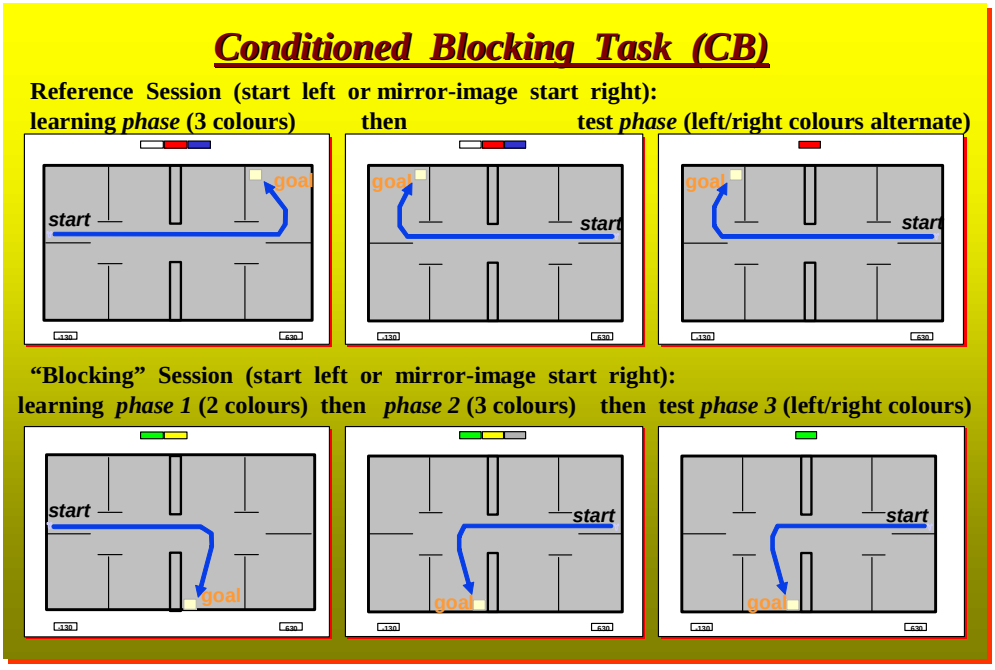

Figure 1: Schematic drawing of the task situation for measuring conditioned blocking – the reference session above and the blocking session below (with the added colour panel in the middle example). The cursor appears on the left or the right (examples left and centre). Three colour panels (conditioned stimuli) are shown in the upper middle of each. The potential direct route to the goal location is illustrated by an arrow. Counters for the plus and minus points awarded for success and delay in finding the goal are shown below the maze.

In practice, to achieve a reasonable information load two such discrimination tasks each with a different goal-locus were run at the same time, in pseudo-random order. The cue for starting a trial and for association with the correct goal locus consisted of colour-panels located above the floor-plan for 2 sec at the start of each trial (see Fig. 1). CB requires that during learning a stimulus is added (e.g. B to A). Thus on such a *"blocking session*" two colour-panels (= A) were presented up to a learning criterion of 5/8 correct responses, when a third colour-panel (B) was added up to full acquisition (7/8 correct). But "blocking" can only be judged by reference to response latencies acquired when all 3 panels were present from the beginning. Thus a second "*reference session*" with 3 different colour panels present from the start of learning was also administered. Counter-balancing our initial study (Oades et al., 1996b), the reference session here followed the blocking session on the next day, for controls and patients alike. (The success of the replication shows that the order of presentation did not contribute to the CB effect.)

What was the measure of CB used? After achieving the learning criterion there was a sequence of 12 test trials consisting of single presentations of the colours that had appeared on the left or the right of the panel arrays during the learning phase. Subtraction of the latency of response to the 'added' colour-panel from that for the other panel present from the start of learning gave the within-session "blocking" score. Subtraction of the similar value obtained on the "reference session" (right panel minus left panel latency) from those on the "blocking session" gave the actual CB scores used. Thus the "first trial" test measure represents a double subtraction procedure (derived stimulus latencies: [right panel – left panel]$_{blocking}$ – [right panel – left panel]$_{reference}$). We report CB data as the derived latencies for the first "trial-pair" measure that represents the mean of the double-subtraction procedures for the first test trials of each of the two discriminations.

NEUROPSYCHOLOGICAL TASKS

The battery consisted of 10 neuropsychological tasks. The **verbal fluency** test (Benton & Hamsher, 1989) requires the generation of as many words as possible starting with the letter F, A or S (1 minute each). In the **trail-making** test (TMT) subjects are asked to join up in sequence first a series of numbers (form A), then an alternating series of letters and numbers (form B, e.g. 1-A-2-B-3, where the score used is the latency B – A; Reitan, 1958). Both tests are thought to reflect functions in the frontal lobe. The **Stroop** test interference score is the increased latency to name the print colour of a word that names a different colour compared to the latencies to name colours and words naming colours. This reflects functions centred on the cingulate cortex. The following two tests reflect broadly parietal function. The **block-design** test requires that a given pattern in the form of a square is reconstructed out of 4 or 9 pieces, in one or two minutes, respectively (Wechsler, 1981). The modified **Mooney faces closure** test requires the classification of the age of degraded images of faces, (Mooney & Ferguson, 1951; Lansdell, 1970). As a reflection of temporo-parietal function, the **picture-completion** test asks the subject to mark the missing feature on a picture of an everyday scene (e.g. a handle on a door, Wechsler, 1981). **Visual reproduction** and **logical memories** were tested in the immediate- and delayed-recall forms (i.e. with zero or 30 min delays: Wechsler, 1987). A series of visual patterns or two short stories are presented for recall, and reflect right- and left-sided temporal lobe function in the areas of visuo-spatial and verbal memory, respectively. In addition the short 12-item form of the **Advanced Progressive Matrices** (APM) was used as a measure of IQ, where scores <6 are below and scores of 12 are above average (Raven 1976). Each item presents a choice of 6 patterns for matching the part missing from a probe pattern. Handedness was scored for 12 activities that are usually lateralised according to the Edinburgh inventory (Oldfield, 1971, +24 for right- and –24 for left handedness).

LABORATORY PROCEDURE

After an overnight fast, a blood sample was taken at 08.00 in the morning (±30 min) before medication. The sample was taken to the laboratory, centrifuged for 10 min at 2000g and the serum stored at –70°C until analysis. The antipsychotic drug level in serum was estimated according to Rao (1986) with a radioreceptor assay technique using ^{3}H-spiroperidol as ligand with increasing concentrations of haloperidol and a DA D2-receptor preparation from the striatum of pigs. The result was expressed as DA D2-receptor antagonist binding activity in relation to the haloperidol standard in neuroleptic units (NU). One neuroleptic unit was defined as the extent of displacement produced by 100 µl of serum containing haloperidol at a concentration of 1 nmol/ml (0.37 ng).

The lower limit of detection for antipsychotic drugs (e.g. haloperidol) in serum was 1 NU (0.37 ng/ml). The intra- and inter-assay coefficients of variation were 5% and 8%, respectively. A regression analysis for the relation between the serum DA D2-receptor antagonist binding activity and the concentration of the antipsychotic drugs gave correlations varying between 0.7 and 0.9. Thus the serum DA D2-receptor antagonist binding activity may be regarded as representative of the antipsychotic serum concentration normalised as neuroleptic units and is a measure of the bioavailability of the drug. As a rule, when patients are in a steady-state with regard to their antipsychotic medication the intra-patient variation of the serum antipsychotic concentration yields a coefficient of variation of 10-15%, that is thus considered to be rather stable. In the following analyses medication data (CPZ, NU, D2-occupancy) were only considered from subjects proven to have taken medication by a positive serum NU value. This resulted in dropping 9 non-compliant patients from the analyses.

Central DA D2 receptor-occupancy was inferred from the antipsychotic dose versus D2-receptor occupancy as reported in the literature (Table 2). A linear regression analysis was performed separately for each drug relating dose to occupancy. Thus, the approximate percentage occupancy for a given dose was computed from the occupancy regression line (see examples for haloperidol and clozapine in Fig. 2). Occupancy could not be calculated for drugs for which there were no published PET data[1]. There are too few published data available to enable direct computations of D2-receptor occupancy from antipsychotic serum levels. Occupancy data were available from 76 patients (Fig. 3).

STATISTICS

Group data were analysed with respect to measures of CB, neuropsychological performance, antipsychotic drug dose, serum level and DA D2-occupancy by multivariate analysis of variance. For task-performance IQ and age were entered as covariates. These analyses are known to be robust in the face of violations of homogeneous data distributions. While CPZ measures showed a normal distribution in the range 1-1700 (χ^2 1.35, p = 0.72, Kolmogorov-Smirnov d = 0.075), the anti-psychotic serum levels and D2-occupancy measures derived from medication were skewed to the left and right, respectively (Kolmogorov-Smirnov d = 0.21 p = 0.01 and 0.17, p = 0.05). Thus group comparisons for these measures are presented with ANOVA and Mann-Whitney U-tests (Table 3). Standard linear regression analyses of the contribution of medication-related data to psychological performance measures used natural log transformed data for NU and D2-occupancy (χ^2 6.13, p=0.11).

Figure 2

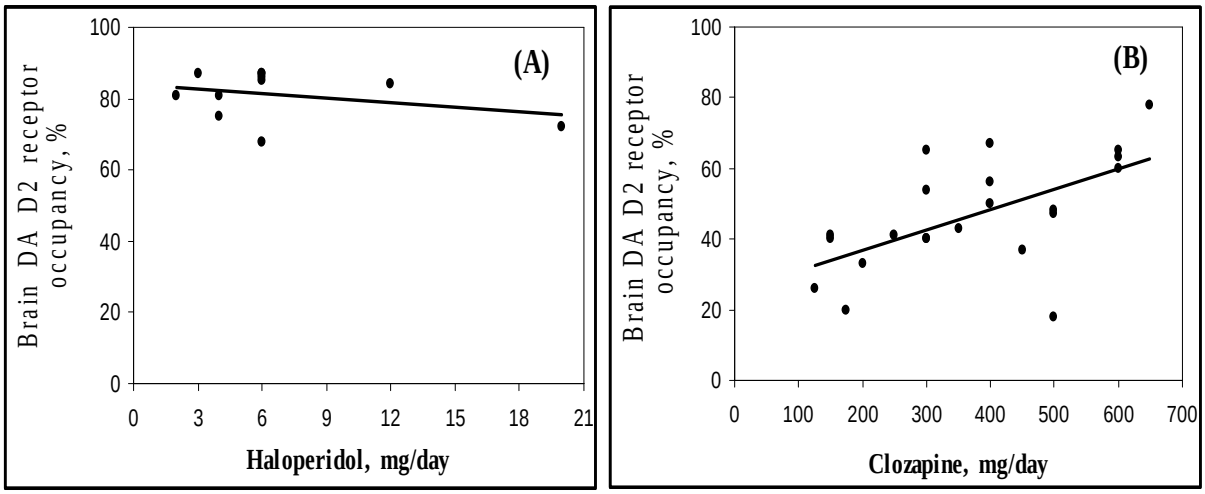

Figure 2: Linear regression of the percentage brain dopamine D2 receptor occupancy with dose of antipsychotic drug based on PET analyses in patients treated with (A) haloperidol, (B) clozapine. (Data in the figure are taken from the references cited in table 2)

Table 2

Reference list for DA D_2-receptor occupancy data

Antipsychotic Drug	References		
Haloperidol	Farde et al., 1989, 1992; Knable et al., 1997.	Wiesel et al., 1990;	Seeman & Kapur, 1997;
Risperidone	Knable et al., 1997	Nyberg, et al., 1999,	Remington, et al., 1998.
Flupenthixol	Farde, et al., 1989, 1992;	Wiesel FA, et al., 1990.	
Clozapine	Farde, et al., 1989, 1992; Pickar, et al., 1996;	Wiesel et al., 1990; Seeman & Kapur, 1997.	Nordström, et al., 1995;
Olanzapine	Nyberg et al., 1997;	Nordström, et al., 1998;	Raedler, et al., 1999.

[1] PET data were not available at the time the regression analyses were calculated for the following antipsychotic drugs that were administered to at least one patient: bromperidol, chlorprothixene, fluphenazine, levomepromazine, perazine, promethazine, sulpiride, sertindole and zotepine.

Table 3

Three measures of antipsychotic medication and its dopaminergic binding parameters - Dose (CPZ equivalents), serum level (NU) and estimated dopamine D2 receptor-occupancy - in male (M) and female (F) patients with schizophrenia and subgroups divided by diagnosis (paranoid, nonparanoid), symptom clusters (thought disorder and ideas-of-reference) and CB-task learning: (standard deviation in parentheses).

Antipsychotic Measure	Dose (CPZ Equivalents)		Serum Neuroleptic Level (Units NU)		DA D2-receptor Occupancy (%)		N
Patient Groups							
Schizophrenia (SCH)	713	(327)	29.3	(29.8)	65.2	(17.6)	76
M	719	(351)	20.2	(14.8)	61.4	(19.2)	45
F	681	(315)	**41.8**[a]	(40.4)	**68.6**[a]	(14.1)	31
Diagnosis Subgroups							
Paranoid (PN)	700	(329)	27.3	(20.2)	**68.2**[b]	(15.2)	55
M	709	(337)	21.5	(13.6)	65.9	(16.5)	31
F	688	(325)	**34.9**[c]	(24.8)	**71.2**[d]	(13.0)	24
Nonparanoid (NP)	746	(328)	34.5	(46.8)	57.2	(15.9)	21
M	790	(355)	19.0	(17.2)	55.9	(16.6)	14
F	657	(270)	**65.4**[e]	(70.5)	59.9	(15.3)	7
Median-split Symptom Clusters							
Ideas-of-reference (High[1])	**789**[f]	(312)	27.5	(18.3)	64.4	(15.4)	35
(IoR) (Low)	647	(329)	30.9	(37.1)	65.8	(16.8)	41
Thought-disorder (High[2])	746	(328)	29.0	(23.3)	66.2	(14.9)	38
(Low)	679	(328)	29.6	(35.5)	64.1	(17.3)	38
Task-acquisition groups							
CB-task acquired	652	(342)	21.4	(15.6)	66.9	(16.8)	42
M	691	(347)	17.5	(11.4)	64.0	(17.7)	30
F	556	(322)	**31.3**[h]	(20.5)	73.9	(12.3)	12
CB-task not acquired	787	(297)	**39.0**[g]	(39.3)	63.0	(15.1)	34
M	821	(321)	27.1	(18.6)	60.2	(15.9)	15
F	760	(282)	48.4	(48.4)	65.3	(14.4)	19

Data from 106/108 patients on antipsychotic medication, of whom 97 were shown to be compliant: the number of patients (N) providing full data sets for the three measures is shown on the right.

1. Low scores = 2 or less, high scores 3-13; **2**.Low scores = 6 or less, high scores 7-28:

		Two- and one-way ANOVAs, covarying for age,						**Mann-Whitney U-tests**		
		dF	F	p	dF	F	p	U	z	p
a	SCH F > M	NU/occupancy	*3,71*	*5.95*	*0.001*;	1,73	9.1/5.4	0.003/0.02,	835/570	-2.8/-1.6	0.004/0.1
b	PN>NP	occupancy	*3,72*	*2.93*	*0.039;*	1,74	5.2	0.025,	353	-2.6	0.009
c	PN F > M	NU	*3,50*	*3.29*	*0.028;*	1,52	5.1	0.029,	498	-1.4	0.1
d	PN F > M	occupancy	*3,50*	*3.29*	*0.028*;	1,52	4.8	0.033,	315	-1.0	0.3 (NS)
e	NP F > M	NU	NS			1,18	5.0	0.039,	197	-2.9	0.004
f	IoR + > -	CPZ	NS			1,74	5.6	0.021,	925	-1.8	0.07
g	not-learn > learn,	NU	*3,72*	*2.86*	*0.04;*	1,74	6.0	0.017,	829	-2.7	0.008
h	learners F > M,	NU	*3,38*	*5.41*	*0.003;*	1,40	7.5	0.009,	184	-2.5	0.01

(NS = not significant)

RESULTS

Data are presented on the antipsychotic drug dose (CPZ), the serum antipsychotic drug DA D2-binding concentration and the central DA D2-receptor occupancy for the patient group as a whole and for the subgroups with paranoid and nonparanoid diagnoses (subsections 1 and 2). We then go on to describe the relationships of these measures to CB and to the performance on a battery of 10 neuropsychological tests (subsections 3 and 4).

1. Relations between antipsychotic drug dose (CPZ), antipsychotic drug serum concentration (NU) and central DA D2-occupancy

A standard linear regression ($F[2,73] = 3.7$, $p = 0.03$, $R^2 = 0.09$) showed that the patients' antipsychotic drug dose (CPZ) related to the serum concentrations expressed in neuroleptic units (ln NU: n = 76, partial correlation 0.3, $p = 0.001$). However, there was no significant relation with central D2-receptor occupancy. Yet restricting consideration to patients treated with atypical or atypical and typical neuroleptics (n=47) showed that a significant proportion of the variance in central D2-receptor occupancy ($F[2,44] = 3.6$, $p < 0.04$, $R^2 = 0.14$) was explained by the antipsychotic dose (partial correlation 0.30, $p = 0.036$). The significance of the regression increased for patients treated only with atypical antipsychotic drugs (n=35). In contrast a consideration of typical drugs (n=29) or even risperidone alone (n=12) did not show a significant relationship. Reasons for this initially surprising result probably reflect the interaction of two features. The normalised measures of the daily drug dose (CPZ) are based on the relationship between the clinically effective dose and measures of the half-saturation of the DA D2 receptor. But as shown in figure 2 (left) there is a ceiling effect for the relationship between central D2 occupancy and the frequently administered dose of antipsychotic drug (e.g. a dose of only 6 mg/d haloperidol results in 80% saturation of central D2 receptors). This introduces considerably more error in to relating D2 occupancy to clinical efficacy than is evident in the relation for clozapine shown on the right of the figure. Nonetheless, we decided to combine the data from all patients in the current, first analyses of the relationships of each medication-related parameter with the measures of behavioural performance.

2. Patient-group differences in anti-psychotic drug dose (CPZ), antipsychotic serum concentration (NU) and central DA D2 receptor-occupancy

A division of the patients according to a diagnosis of paranoid vs. nonparanoid schizophrenia showed that those with a paranoid diagnosis had a significantly higher level of central D2-occupancy (19%) than those with nonparanoid diagnoses (b in table 3). This difference was not reflected in the dose nor the serum level of antipsychotic drug activity. (These groups did not differ significantly in the PANSS ratings of positive, negative or general symptoms.)

Patients with high scores for symptoms of ideas-of-reference and thought disorder tended to receive higher doses of medication (f in table 3), but there was no evidence of differences in serum or central measures. However, patients who did not learn the CB task adequately showed higher circulating levels of antipsychotic D2-binding activity (g in table 3). It is striking that female patients, independent of the subgroup diagnosis, usually showed higher levels of both serum antipsychotic activity and central D2-occupancy (a, c, d, e, h in table 3).

3. Schizophrenia: subgroups and CB

Analysis of the 62 patients who learned the CB task with a two-way MANCOVA with age and IQ as covariates showed impaired CB for nonparanoid patients with respect to those with a diagnosis of paranoid schizophrenia (+3.1 SD 7.5 vs. –1.1 SD 7.3: $F[2,53] = 3.5$, $p = 0.022$). This impairment dissipated with learning across test presentations (repeated trials analysis, $F[2,108] = 5.2$, $p = 0.04$: Bender et al., 2000).

Regression analyses for the contribution of medication-related parameters to CB did not obtain conventional levels of significance for either the patient group as a whole nor the

paranoid subgroup. For the 11 nonparanoid patients with an adequate CB performance and a full set of medication-related measures, increases of D2-occupancy related to decreases of CB (partial correlation –0.73, p = 0.02). In contrast, increasing serum concentrations of D2-binding activity related to the recovery of CB on later test-trials (partial correlation +0.78, p = 0.01). As the sample size for these analyses was small (F [3,7] = 4.3 and 9.3, p = 0.05 and 0.008, R^2 = 0.65 and 0.80, respectively), the result is tentative. Thus the MANOVA analysis of CB was repeated for the *whole* patient group using central D2 receptor-occupancy as a covariate. This procedure removed the significance of the result (one-way analyses, F = 5.1 *vs*. 2.0). As the use of the antipsychotic dose or serum levels did not affect the analysis it may be concluded that the degree of central DA D2-occupancy contributed to the variance of CB.

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Table 4

Significant regression analyses for antipsychotic drug dose (CPZ equivalents), serum antipsychotic level (NU) and dopamine (DA) D2-occupancy on neuropsychological performance for patients and patient subgroups.

Antipsychotic drug dose (CPZ equivalents)			
All patients	F (10, 65) = 3.4,	p = 0.001,	R^2 = 34.2
Paranoid	F (10, 44) = 2.8,	p = 0.009,	R^2 = 38.7
Low Ideas-of-Reference	F (10, 30) = 2.2,	p = 0.048,	R^2 = 42.0
High Thought-Disorder	F (10, 27) = 2.9,	p = 0.012,	R^2 = 52.1
Antipsychotic serum level (NU)			
All patients	F (10, 65) = 2.7,	p = 0.009,	R^2 = 29.0
Paranoid	F (10, 44) = 2.9,	p = 0.007,	R^2 = 39.7
High Ideas-of-Reference	F (10, 24) = 2.7,	p = 0.024,	R^2 = 52.6
High Thought-Disorder	F (10, 27) = 2.7,	p = 0.02,	R^2 = 49.6
Central DA D2-receptor occupancy			
All patients	F (10, 65) = 2.5,	p = 0.012,	R^2 = 28.0
(Paranoid	F (10, 44) = 1.6,	p = 0.13,	R^2 = 27.1)
Low Ideas-of-Reference	F (10, 30) = 2.6,	p = 0.02,	R^2 = 46.3
Low Thought-Disorder	F (10, 27) = 2.8,	p = 0.015,	R^2 = 51.3

1. Neuropsychological performance assessed for 10 tasks (one measure each, see text for details).
2. R^2 represents the variance in performance of the neuropsychological tasks by the patients or patient subgroup listed explained by the medication parameter.
3. The subgroups considered were those with a diagnosis of paranoid or nonparanoid schizophrenia and those with high or low ratings for ideas-of-reference or thought disorder divided by a median split
4. See table 5 for tasks with significant partial correlations
NU = neuroleptic unit: CPZ = Chlorpromazine

Table 5

Partial correlations (r) and significance (p) for antipsychotic drug dose (CPZ equivalents), serum antipsychotic level (NU) and central DA D2-occupancy, with neuropsychological test performance in patients (left) and patient subgroups (centre and right).

Antipsychotic drug dose (CPZ equivalents)

	All patients (n=76)		paranoid (n=55)		low IoR (n=41)		high ThD (n=38)	
.	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Trail-making (TMT B-A)					-0.30	0.09	-0.33	0.08
Mooney Faces	-0.36	0.002	-0.43	0.003	-0.32	0.07	-0.47	0.01
Picture Completion	-0.28	0.021	-0.36	0.015	-0.36	0.04	-0.55	0.002
Block Design	+0.30	0.015	+0.35	0.018			+0.40	0.03
Copy Immediate	–0.24	0.048					-0.35	0.06

Antipsychotic serum level (NU)

	All patients		paranoid		high IoR		high ThD	
.	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Trail-making (TMT B-A)	-0.22	0.07					-0.39	0.035
Stroop Interference	+0.37	0.002	+0.43	0.003	+0.43	0.030	+0.50	0.006
Mooney Faces					-0.48	0.013		
Picture Completion	-0.35	0.004	-0.42	0.003	-0.61	0.001	-0.50	0.005
Block Design			+0.29	0.054	+0.55	0.004		
Copy Immediate	-0.26	0.034	-0.30	0.044	-0.42	0.032		
Copy Delay	+0.26	0.034	+0.27	0.070			+0.37	0.050

Central DA D2-receptor occupancy

	All patients		(paranoid)		low IoR		low ThD	
.	**r**	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Verbal Fluency	-0.33	0.007	-0.33	0.026				
Mooney Faces							+0.41	0.026
Copy Immediate							+0.43	0.021
Logical-memories Immediate	-0.24	0.055			-0.47	0.006	-0.58	0.001
Logical memories Delay	+0.35	0.003			+0.58	0.001	+0.61	0.001

1. The subgroups considered were those with a diagnosis of paranoid or nonparanoid schizophrenia and those with high or low ratings for ideas-of-reference (IoR) or thought disorder (ThD) divided by a median split. 2. Regression models were only significant for the subgroups listed. [The result for paranoid patients with DA D2 receptor occupancy showed only a trend significance p=0.1, see table 4] NU = neuroleptic unit: CPZ = Chlorpromazine

4. Schizophrenia Subgroups: Neuropsychology

Group comparisons showed that patients were impaired significantly with respect to controls on 8 of the 10 neuropsychological tests (i.e. not the Mooney faces and Stroop interference tasks, Oades et al. in submission). Antipsychotic dose, serum levels and central D2 receptor-occupancy were entered into standard regressions to identify the influences of the medication parameters on the performance differences. Relationships of the antipsychotic dose (CPZ) with psychological test performance would be expected to reflect the effects of the drug as a dopaminergic antagonist on DA D2 binding sites and its influences on the activity in other transmitter systems (e.g. anticholinergic activity of atypical neuroleptic drugs: such influences can be inferred by a difference in the sign of the relationship of the medication parameters with the performance of specific tasks, table 5). Only the influences that reflect specifically DA bioavailability should be seen in the relationships with serum levels of DA D2-binding activity and central D2 receptor-occupancy. Dopaminergic effects on performance were evident as a number of significant linear regression analyses were found for the entire patient group with each medication-related parameter. The specificity of the relationships to subgroups of patients was explored and only the significant results are listed in table 4 and 5.

The regression results in table 4 showed that of the variance in neuro-psychological performance explained by DA-related parameters most was attributable to the measures of serum neuroleptic units (NU) and central DA D2-occupancy (28-29%). The additional variance explained by the drug dose (CPZ) that may include some non-DA-related activity, was small (up to a total of 34%). With regard to the subgroups, regression analyses for the nonparanoid patients produced no significant results. For the patients with a paranoid diagnosis the similarity of R^2 for the dose (CPZ) and the serum levels of antipsychotic drug (NU) suggest that DA-related activity was important for their neuropsychological performance. Anal-yses for patients divided by a median split on the ratings of ideas-of-reference or thought disorder varied with respect to whether the high or low scores showed significant relationships: compare the R^2 (high IoR) of 52.6% for NU with the R^2 (low IoR) of 46.3% for D2-occupancy. This characteristic, along with the near significant results obtained for groups rated on both sides of the median, suggests that divisions according to these symptom parameters did not show an important dichotomy of the influences of medication-related activity.

A comparison of the partial correlations for test performance with the medication-related parameters in table 5 shows 3 results. First it should be noted that the partial correlations between a medication parameter and performance on specific tasks are consistent in their direction of correlation from the patient group as a whole across the patient subgroups in the table. Secondly, as discussed above, similarities in the *direction* of the correlation between the medication parameters (e.g. CPZ and NU) are consistent with an interpretation in terms of a DA influence (e.g. negative for TMT B-A and picture completion, but positive for block-design). In contrast, a difference in sign of the correlation (e.g. for Mooney faces and immediate visual reproduction for CPZ vs. D2-occupancy) suggests there are separate influences mediated by DA and by non-DA activity. Lastly, unique is the negative relationship of verbal fluency and the positive relationship of *delayed* logical memories with D2-receptor occupancy (table 5, bottom). These correlations were not altered by consideration of the severity of positive, negative and general symptoms, (only the antipsychotic dose, CPZ, increased with ratings of positive symptoms [partial correlation +0.25, $p < 0.04$]).

DISCUSSION

This study is unusual for relating serum levels of medication in patients with schizophrenia

to neuropsychological measures of their abilities. It is the first study of its kind to attempt to relate antipsychotic dose, serum level and DA D2-occupancy in patients with schizophrenia with multiple measures of their performance on tests of selective attention and cognition.

Our first aim was to assess quantitatively levels of DA D2 antagonist binding activity circulating in patients treated with antipsychotic drugs, being sure about compliance and taking individual pharmacokinetic variability into account. These measures are important from a clinical point of view, in that to a degree the DA D2-blocking potential of different antipsychotic drugs relates to clinical efficacy (Hess et al., 1987), but that there is a threshold above which the likelihood of extrapyramidal side effects increases disproportionately (Tauscher et al., 1999).

In the context of sub-group differences according to the type of symptoms expressed and the diagnosis and there were three major findings. First there were no differences in serum levels or central D2-occupancy between patients expressing high or low degrees of thought disorder or Schneiderian ideas-of-reference. But patients with much thought disorder tended to receive higher levels of antipsychotic medication. Second, female patients independent of subgroup diagnosis showed higher serum levels of antipsychotic drug and central DA D2-occupancy. Third, the putative central DA D2-occupancy, calculated on the basis of published PET data, was higher in patients with a paranoid than those with a nonparanoid diagnosis.

Accordingly, one could posit three putative consequences, respectively, that should be tested. First the prominence of thought disorder among symptoms encourages the administration of high doses of antipsychotic drugs. In view of evidence implicating unusual serotonin function in thought disorder perhaps antipsychotic drugs with a marked serotonergic profile would be more appropriate (Bender et al., 1999). Second high serum levels of antipsychotic drugs with DA D2-binding activity in female vs. male patients may reflect gender-specific pharmacokinetic differences. These differences may arise as a result of the lower body weight of females and the lower proportion of female patients who smoke. (Increased smoking is known to induce enzyme activity in the liver responsible for the metabolism of antipsychotic drugs that leads to lower levels of the antipsychotic drug in the circulation, for a review see Batra, 2000). A further contribution to increased levels of serum D2-binding activity in females could arise from the blocking of DA D2-binding by steroid hormones (Di Paolo, 1994).

Thirdly, increased D2-receptor occupancy in paranoid patients is a consequence of increased DA activity in this subgroup of patients. This is consistent with our prediction based on post-mortem studies and the increased responsiveness of paranoid patients to neuroleptic therapy. Increased D2-occupancy would be expected, as under current practice these patients are likely to receive typical antipsychotic drugs first and to show some clinical response to them. The PET data show that these typical antipsychotic drugs exhibit higher degrees of central DA D2 receptor occupancy than atypical antipsychotic drugs (table 2). Direct evidence has also been provided with studies of the effects of psychostimulant administration (Bilder et al., 1992; Laruelle et al., 1999). Laruelle and colleagues demonstrated an increased responsiveness of such patients to amphetamine challenge at the level of the DA receptor, DA activity and the symptoms expressed (Laruelle *et al.,* 1999).

Our second aim in this study was to explore the possibility of relationships between impaired measures of selective attention and various neuropsychological abilities with measures of DA-related activity reflected by serum levels of antipsychotic drug D2-binding activity or putative central DA D2-occupancy.

Conditioned Blocking (CB)

Patients who had difficulty in learning the associative learning task did not differ in the level of positive, negative or general symptoms expressed from those who learned the task successfully (Table 1). They had

higher serum levels of antipsychotic drug, although they did not show any differences in central DA D2-occupancy measures in comparison with those who learned the task. The occupancy result probably reflects observations from the PET studies from which the measures were derived, namely that saturation of the DA D2 receptor occurs rapidly, especially following administration of typical neuroleptics, and thus differences were not discernible. The increased serum levels may reflect other unknown pharmacokinetic features that underlie decreased psychological or clinical response to antipsychotic medication, but not simply symptom severity, as noted above.

Among those who learned the task, patients with a nonparanoid diagnosis showed reduced CB. They learned about all the stimuli presented during the acquisition and the test phase. This is interpreted as a persistence of a controlled information-processing learning strategy normally present at the start of task-learning. Usually stimulus processing and response become automatic with the acquisition of a learning criterion. High CB scores of paranoid patients late in the test suggest they were slow to switch back to a controlled processing mode for learning about the individual panels. Normal or superior performance in paranoid vs. impairments in nonparanoid patients (or similar positive/negative symptom groups) have been reported for other studies of attention-related processing such as backward masking (Williams and Gordon, 2000 and references therein).

CB has been reported to be associated positively with DA utilisation (Oades et al., 1996a,b) on the basis of urine measures. This is consistent with lower levels of utilisation and metabolite levels in nonparanoid vs. paranoid patients in urinary (Oades et al., 1994) and plasma samples from similar patient groups with negative and positive symptoms (Amin et al., 1999). This in turn is consistent with the present finding of higher levels of central DA D2-occupancy in the patients with a paranoid diagnosis, on the assumption that their higher turnover reflected increased DA D2 binding sites, as was predicted in the introduction. That this plays a role in CB is suggested by the loss of significant differences in CB performance between the subgroups after controlling for this factor.

Neuropsychology

The test battery was selected in order to reflect different cognitive functions attributable to right vs. left hemisphere (e.g. visuospatial vs. verbal abilities) and frontal/parietal/temporal lobe activity (e.g. verbal-fluency, Mooney-faces, story-recall). The most striking association for central DA D2-occupancy was with delayed recall of a short story (i.e. with logical memories performance that reflects largely left temporal lobe function). Increasing occupancy was related to improved recall across all subjects, especially for those showing few ideas-of-reference or little thought disorder. A negative relationship, a detrimental influence of increased occupancy was also recorded for word production reflecting left frontal lobe function.

The present demonstration of a putative DA D2 receptor-mediated role in memory is not surprising in view of the widely reported problems of patients with schizophrenia on tests of recall (e.g. Aleman et al., 1999). However, it should be emphasised that our results are clearly at odds with their presumption that medication had little influence. This, of course, was based on numerous reports of an absence of a correlation for performance with CPZ equivalents that we also describe here. Evidence for DA medication-assisted memory performance (verbal recall, left hemisphere) independent of gender is also consistent with the findings of a review by Spohn and Strauss (1989). They attributed improvement on medication to an increased memory span and the decreased influence of irrelevant features on task performance.

Our finding that the role of central DA D2-occupancy in memory extends to paranoid but not nonparanoid patients is consistent with three different sets of findings. Firstly PET measures of DA D2-occupancy were associated with positive symptoms following

olanzapine treatment (Lavalaye et al., 1999). Secondly impaired recall of verbal passages was associated with increasing plasma levels of the DA metabolite (HVA) in a group of patients mostly diagnosed with paranoid schizophrenia (Gilbertson et al., 1994). Thirdly in such patients high ratings of positive symptoms were associated with increases of recall and recognition errors (Brebion et al., 1999). Such errors are often false alarms (Brebion et al. 1999; Bender et al., 1999) and interpreted in terms of problems with source-monitoring and response criterion. The present results imply that these functions are attributable to fronto-temporal interactions modulated by DA. There is unequivocal evidence for such a mechanism from animal studies. Mesocortical DA input is often on the same spine of frontal pyramidal neurones receiving hippocampal glutamatergic input. Gurden and colleagues (1999) showed that electric stimulation of the VTA, the source of the DA input, enhanced the amplitude and duration of long-term potentiation (acclaimed as a model for memory formation) elicited by stimulation of the hippocampal input. They were able to correlate DA levels with the elicited field potentials.

Our hypothesis that antipsychotic dose would yield correlations with a sign opposite to that for DA D2 occupancy was confirmed modestly for the Mooney faces closure task and immediate visual reproduction (for CPZ vs. D2-occupancy), measures of visuospatial functions reflecting right temporo-parietal function. However, this hypothesis requires further study as the relationships between the other two medication parameters (CPZ vs. NU) were not consistent with our prediction. It is perhaps surprising that we failed to find strong evidence for non-DA mediated impairments resulting from medication. Many neuroleptics have cholinergic and alpha-adrenergic binding properties: antagonism at both of these sites can impair higher cognitive and memory functions (Spohn and Strauss, 1989; Li et al., 1999).

Lastly the associations of antipsychotic drug dose and serum DA D2-blocking activity, negative with trail-making and picture completion but positive with block design could not be specifically predicted. We are not aware of studies directly relating performance on these tests to measures of DA receptor activity. However, from the discussion of memory-related function, above, we would predict that whereas high levels of DA activity might impair functions required for the block-design test, they should be helpful in the requirement of set switching tested by trail-making (TMT B-A).

The present report should be regarded as one that raises working hypotheses about putative DA-D2 receptor-mediated function in attention and recall for future testing. The present data were limited by the availability of central DA D2-occupancy data for only five of the more commonly prescribed antipsychotic drugs and the relatively crude estimations of occupancy possible for typical antipsychotic drugs: inclusion of data from more PET studies on a wider range of antipsychotics would extend the data basis considerably. The tentative interpretations of the measures of serum DA D2 blocking activity and estimations of central DA D2 occupancy in terms of hyper- or hypoactivity will benefit from measures of the monoamines and metabolites circulating in these patients.

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