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Stimulus dimension shifts in patients with schizophrenia, with and without paranoid hallucinatory symptoms or obsessive compulsive disorder: strategies, blocking and monoamine status

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Abstract

Reversal, and intra-dimensional (ID) and extra-dimensional (ED) non-reversal discrimination shifts were studied to see if learned inattention to the irrelevant dimension differentially influenced the efficacy of learning and stimulus choice strategy. Performance was compared with conditioned blocking (CB) and monoamine metabolic status between healthy controls, patients with obsessive compulsive disorder (OCD) or schizophrenia with (PH) or without (NP) active paranoid hallucinatory symptoms.

PH and NP patients improved learning with practice, but showed an impaired shift on each task. OCD patients were impaired only on the ED-shift. The NP patients' impairment was nonspecific and, unlike PH and controls, it related to reversal performance. All subjects acquired an attentional set for colour reflected in the length of stimulus-response sequences. Analysis of paired-stimulus choice-strategies showed that while all patients showed fewer correct win-stay choices, only PH patients perseverated with lose-stay choices. Learning about the added stimulus in the CB task related to ID-shift efficiency in NP patients. Increases of dopamine activity related to delayed learning but more switches of stimulus choice in the shift-tasks. Increases of serotonin activity correlated with faster learning in controls, OCD and PH patients. In NP patients the opposite held for dopamine and serotonin activity.

Thus the two learned inattention tasks have different if related requirements and correlates: the data are consistent with the use of automatic exogenous attention strategies by NP patients, of inefficient controlled attention by PH patients and the automatization of endogenous processes in controls.

Keywords: Attention; Reversal non-reversal; Conditioned blocking (CB); Strategy; Dopamine (DA); Serotonin (5-HT); Schizophrenia; Obsessive-compulsive-disorder (OCD)

1. Introduction

Learned inattention is a paradigm for studying the influences of experience of stimuli or learned associations on learning about new stimulus-response contingencies. It includes three types of task: latent inhibition (LI, [27]) reflects the influence of the familiarity of a stimulus with no important consequence on the speed of its forming new associations; conditioned blocking (CB, [25]), examines the influence of a relatively familiar stimulus-response association on the speed of forming the same association for a new stimulus element; intra-/ extra-dimensional shift (ID/ED-shift [26,55]) juxtaposes three tests of the sorts of processes likely to be occurring in LI and CB.

What are these 3 kinds of shift-tasks? The first is a reversal that follows discrimination between 2 stimuli varying on 2 dimensions (e.g. form and colour). The same stimuli are used as in the initial discrimination, but after reaching criterion (e.g. blue not yellow, is correct) the opposite contingency is introduced. In the implicit form the change occurs without warning (e.g. yellow is now the target). In the ID-shift new stimuli in the same dimension are introduced at criterion, (e.g. target from pink to lilac vs. non-target from blue to turquoise). On the ED-shift the same

stimuli may be used but there is a change of target dimension (e.g. from colour to form).

In animals as well as humans the ID is easier to learn than the ED version [48, 54]. The ID score measures the ability to develop an attentional set (e.g. for colour), while the ED score is a measure of the ability to switch from such a set [44, 48]. This procedure has long been held to be sensitive to attentional abilities [29]. From this theoretical back-ground, the ID-shift is akin to the CB task and performances should be related. In contrast, the ED-shift requires an alteration of set, the ability to switch between the dimensions pertinent to the task. The ED-shift resembles a reversal, in that both tests use the same stimuli in initial learning and after the shift, but differs in that reversal requires rejection of the set and de novo learning.

What brain systems might be involved in these types of attention shift? In humans deficits restricted to the ED-shift (i.e. perseveration) have been reported after frontal lobe excision but not after temp-oral lobe or amygdala-hippocampal brain damage [43, 44]. This was confirmed with quinolinic lesion of the Marmoset prefrontal cortex and an interesting dissociation was reported [8]: orbito-frontal damage impaired the ID- shift (not significant) and the reversal task significantly. With regard to neurotransmitter systems, excitotoxic lesion of frontal cholinergic innervation was reported to impair discrimination and reversal but not ID:ED-shifts in the Marmoset [49]. A study of the role of noradrenaline (NA) concerned rats with toxic lesions of the dorsal noradrenergic bundle [28]. They claimed that NA depletion facilitated the ID-shift. How-ever this result has been questioned, as the lesion group also required twice as many trials to acquire the initial criterion

An early study of the dopamine (DA) releasing properties of amphetamine in rats showed an improvement of reversal learning but not on ED-shift in light-dark vs. position discriminations in a Y-maze [60]. The effect on reversal is consistent with enhanced attention or a facilitation of switching response strategies, but the lack of effect on the ED task makes generalization difficult. Toxic lesions of the frontal DA system in primates tended to enhance ED-shift [13], but the effect was not robust and many controls also perseverated. The result could implicate fronto-striatal function in ED performance, but it is not clear if changes reflected increased cortico-subcortical DA function (and thus, more switching) or decreased DA function in the frontal lesioned areas.

A normally functional DA system seems important for the ED-shift in man: patients with Parkinson's disease are impaired in ED performance, but those responding to L-DOPA treatment showed some improvement [11, 24, 44]. Other patient groups studied include childhood autism [21] and schizophrenia [12]. Autistic patients were described as showing a mild ID and a severe ED deficit. The schizophrenia sample also had more problems with the ED than the ID-shift, but they were not easy to test, with 40% having difficulty in learning one of the tests. Reversal performance was normal so long as the IQ was normal.

Given that patients with schizophrenia are reported to show impaired LI [4] and CB [22, 23, 40] the main purpose of this study was to see if they also had problems on the shift tasks. The analysis sought to determine on which shift tasks there was a deficit and what its nature was. Could equivocal results on shift- tasks [12] be resolved by separate consideration of patients with (PH) and without paranoid-hallucinatory symptoms (non-paranoid patients, NP) and analysis of their stimulus-response patterns? Could function or dysfunction be related to the performance on CB and associated monoamine metabolic status, as theory would predict (above), where we have already reported on CB and monoaminergic back-ground activity in the same individuals [40].

As schizophrenics have been described as less constrained by past regularities, one would predict that shifts of attention would be facilitated in these patients [19]. However, as disrupted CB (facilitated shift) was found to be largely restricted to NP patients, we would predict that this would be reflected in their ID-shift and that their ID and CB performance would be related [40].

PH patients were predicted to show less and NP patients more of an impairment on the ED-shift on the basis of (a) animal studies, (b) the helpfulness of parkinsonian medication, (c) the relationship between CB performance in controls and urinary measures of basal DA activity [39,40]. Relevant to this pre-diction is that PH patients show more DA activity and are more responsive to neuroleptic medication [38] while an impairment has been noted in clinically less responsive clozapine-treated patients [12], likely to be symptom-atically related to our NP group.

These predictions are also based on an earlier synthesis proposing a role for DA activity in the ability to switch and NA activity in tuning between channels pro-cessing information [35] and serotonin (5-HT) in the volume control of salient stimuli. To follow this up, an analysis of response sequences to particular stimulus dimensions was performed, as a measure of perseveration analogous to that performed in card-sorting tests, and an analysis of pairs of response choices was performed to see if subjects applied the standard leaning rule of 'win-stay'/ 'lose-shift'. (This rule reflects the 'law of effect', namely that subjects usually per-form more rewarded and fewer non-rewarded behaviours [10]). On the basis of effects with CB, inter-actions for NP performance of ID-shift with DA and 5-HT activity was anticipated.

2. Methods

2.1. *Subjects*

Data for 28 patients with schizophrenia (SCH), 13 patients with obsessive compulsive disorder (OCD) and 29 healthy controls (CON) are reported. Schizophrenia and OCD were diagnosed by two clinicians and two psychologists in 43 admissions (DSM IIIR). Only two of these were unable to learn the tasks. Exclusion criteria included other m ajor illnesses, substance abuse or an IQ less than 70 (Raven's standard progressive matrices). The only comorbid diagnosis was trichotillomania in one case of OCD. SCH patients were interviewed and rated on the scales for assessment of positive and negative symptoms (Spearman rho= 0.64–0.75, 4 raters on 64 questions [2, 3]). A median split at a score of 7 for hallucinations and delusions separated a group with active positive symptoms (PH, *n*=14, age range 15–24y): they did not differ significantly from the non-paranoid group (NP, *n*=14, age range 12–24y) on the incidence of negative symptoms. Symptom severity was also scored on the Brief Psychiatric Rating scale (BPRS [42]; Table 1).

Healthy controls (age range 12–24y) were paired for gender and age within 4 months with the SCH patients and one extra one was taken to match a young patient with OCD (age range 11–20y). They reported no psychiatric complaints or major medical problems and were free of medication when tested (demographic details in Table 1). Testing followed approval of the protocol by the clinic management, agreement of the therapists to the tests in each case and the co-operation, understanding and consent of the subject and the legally responsible adult.

2.2. *Task*

Three colour-pattern discriminations, known has the Color-Form-Test or Concept-Formation-Task, were presented on a PC colour monitor with a joystick for response (CFT; [51, 52, 56]). Subjects were instructed to discover by trial and error which of three visual dimensions were correct (colour, form or position). In fact, each (CFT1, 2 and 3) started with a colour discrimination. At the start of each trial a white stimulus panel (18x 7 mm) appeared in the middle of the top half of the screen for 0.5 s to attract central eye fixation. With a stimulus onset asynchrony of 1.1 s, coloured forms appeared in adjacent panels, to the left and right (Fig. 1, left). These were illuminated for 2.0s and the subject was allowed up to 5s to respond. Response with a joystick, sensitive only to left or right touches, directed cursor movement to the end of a 6-cm corridor in the middle of the screen. Positive feedback was given with a yellow shimmer around the cursor, but after an incorrect response a cage appeared around the cursor prohibiting further movement. There was an inter-trial interval of 2.0 s. Subjects were allowed up to 100 trials to acquire the discrimination (88% over 8 trials).

Initial learning in the first task (CFT1) involved a triangle and a cross (i.e. '+'): each form could be blue or yellow on successive trials with the dimensions alternating from left to right in a pseudo-random sequence. The stimuli used in the second and third tasks (CFT2 and 3) are shown in Fig. 1. After learning each initial discrimination there was a shift, without warning to a second discrimination. In CFT1 this was a reversal (e.g. the target was now yellow not blue); in CFT2 there was an ID-shift to slightly different but clearly distinguishable colours and in CFT3 there was an ED-shift from colour to form (brown to a double-pyramid target). Dependent variables were the reaction time (1/100ths of a second, excluding the criterion achieving response sequence), the number of trials to reach criterion; the number and mean length of response sequences with three or more choices repeated to the same dimension (two positions, two colours, two forms) and the decision to repeat (stay) or change (shift) response after (non)reinforcement (i.e. win/lose-stay, win/lose-shift). The procedure was controlled by software used in reports on CB studied in the same subjects [39, 40] and may be obtained from the author.

2.3. *Monoamine analysis*

Dopamine (DA), noradrenaline (NA), serotonin (5-HT) and their metabolites (homovanillic acid, HVA; 3-methoxy-4-hydroxyphenylglycol, MHPG; 5-hydroxy-indole acetic acid, 5-HIAA) were analysed in 24 h urine collections from subjects on a low monoamine diet on the day after the test. Acidified samples were frozen until analysis with ion-exchange liquid chromatography and fluorescence detection. Volume adjusted measures are expressed as ng/g creatinine/m^2 body area to correct for general metabolism and large variations of body size [38].

2.4. *Data treatment*

Reaction time (RT) data for the 3 acquisition and 3 shift task-phases were normally distributed (e.g. original learning, Kolmogorov-Smirnov d=0.039; E/D shift, d=0.110). Normal parametric ANOVA and Pearson (rho) correlation coefficients are reported for all group within session and between session (repeated measures) analyses. But, data for the number of trials to reach the learning criterion on each of these 6 phases were not normally distributed (e.g. original learning, d=0.227, P<0.01; E:D shift, d=0.326, P<0.01). Here, an initial analysis for all SCH patients vs. the OCD and CON groups with the relatively robust parametric ANOVA are followed by non-parametric analysis of the performance of the PH and NP subgroups (i.e. Kruskal Wallis (KW) for within session and Friedman ANOVA with Kendall's coefficient of concordance for between session analysis). Spearman rank correlations are reported for non-parametric data.

The analysis strategy in the results section is, (1) to compare group performance (first trials, then RT) on initial learning (CFT1) and then to compare the 3 initial learning sessions with repeated measures. Having established basic group learning performance, (2) group differences on the reversal were established as a baseline for comparison with ID and ED-shifts (repeated measures then separate consideration of each shift-task), (3) analyses of the lengths of response sequences and types of error indicated the cognitive style or task-solving strategy used, (4) the possibility that the shift and CB tests of learned inattention were related and could be construed to reflect similar processes was explored with correlations, concord-ance and standard regression. Finally, relationships with monoamine activity were explored (Pearson rho, first-order regression).

3. Results

3.1. *Initial discrimination learning* (*CFT*1: *CFT*1 –3)

3.1.1. *Number of trials*.

Both SCH subgroups needed twice as many trials as the comparison groups to learn the initial discrimination (CFT1: significant for SCH and NP; Fig. 2). Covariate analysis of variance showed that neither age nor neuroleptic dose contributed to the increase (for SCH, r=+0.04, r=-0.035, respectively), but IQ as a covariate did reduce the significance of the result (Table 2; cf. r=-0.31, P= 0.01 for all subjects but r=+0.055 for SCH alone).

Table 1

Subject group characteristics

Group:	gender m / f	age years (sd)	SPM IQ (sem)	Education years (sd)	Episode (PH/NP) Duration y (OCD) (sd)	BPRS sum/Q (sem)	Hallucinations (sem)	Delusions (sem)	SANS/ SAPS (sem)	CPZ Neuroleptic (sd)	ACh Biperidene (sd)
PH	9 5	19.6 *3.4*	91 *5*	11.8 *2.4*	2.5 *1.8*	3.3 *0.2*	11.6 *2.2*	17.6 *3.1*	1.8 *0.3*	757 *714*	4.3 *1.8*
NP	6 8	17.5 *3.4*	86 *3*	9.5 *2.1*	1.7 *1.1*	2.6 *0.3*	1.7 *0.6*	2.9 *0.9*	6.7 *1.8*	1069 *1276*	4.8 *1.5*
OCD	9 4	16.3 *2.3*	117 *6*	9.7 *0.8*	2.3 *1.8*						
CON	15	14 *3.6*	18.0 *3*	113 *3.3*	11.5						

BPRS = sum of Brief Psychiatric Ratings scored per question (t=1.84, p=0.08); Symptoms (hallucinations, delusions) rated on the scales for the assessment of negative (SANS) and positive symptoms (SAPS); Medication levels did not differ between the PH and NP groups, CPZ = chlorpromazine equivalents [47]; cholinergic medication (ACh) = biperidene (mg). Controls were age and gender matched to the patient groups, but the PH group was slightly older than the OCD group (t=+2.7, p=0.012). PH and NP groups had lower performance IQ than the comparison groups on Ravens standard progressive matrices (SPM; t=-3.4 to -5.8 p<0.02) but did not differ on the number of years of education.

Table 2

Summary of results (3 groups, SCH/OCD/CON, and 4 groups, PH/NP/OCD/CON)

Task	ANOVA (*F*-test, 3 groups)			Scheffe *P*			ANOVA (Kruskal-Wallis, 4 groups)			M-W	
	F	df	*P*	CON vs. SCH	OCD vs. SCH	CON vs. OCD	H	df (*n*)	*P*	PH vs. CON *U* (*P*)	NP vs. CON *U* (*P*)
Trials to acquire discrimination, original learning											
CFT1											
Learn	9.8	2, 67	0.00002	0.0005	0.014	ns	9.4	3 (70)	0.025	143 (0.12)	90 (0.12)
Covary IQ	5.2	2, 65	0.008	0.0007	0.017	ns					
							Friedman (4 groups)				
CFTI-3 (repeated measures)							Chi	df (*n*)	*P*		
Group	5.3	2, 67	0.007	0.007	ns	ns	9.5	2 (70)	0.008		
Session	1.4	2, 134	ns								
Interax	1.9	4, 131	0.1				See text				
Reaction time, RT, original learning							ANOVA (*F*-test, 4 groups)			Scheffe *P*	
CFT1											
Learn	6.4	2, 67	0.003	0.0035	ns	ns	4.2	3, 66	0.009	0.032	0.085
Covary IQ	6.8	2, 65	0.002	0.0047	ns	ns	4.5	3, 64	0.006	0.050	0.085
CFTI-3 (repeated measures)											
Group	12	2, 67	0.0001	0.001	ns	0.088	7.6	3, 66	0.002	See text	
Session	2.2	2, 134	ns				2.1	2, 132	ns		
Interax	2.0	4, 134	0.09	See text			1.5	6, 132	ns		

CFT1, original learning (session 1); CFT2, learning session 2; CFT3, learning session 3; M-W, Mann-Whitney *U*-test; ns, non-significant; *P*, probability; interax = group x session interaction.

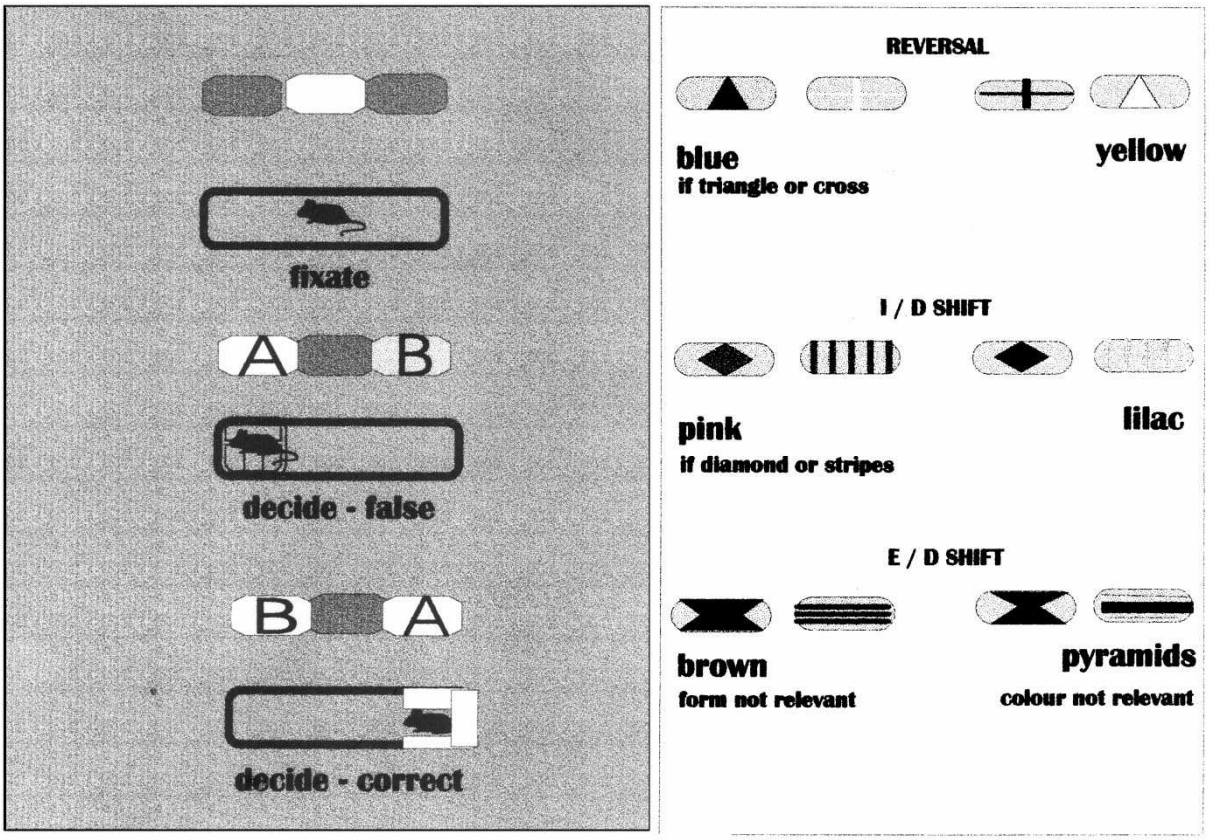

Fig. 1. Scheme to show the task set-up. Left (top): to aid central fixation the middle panel lights up white; (middle) two forms in two colours appear, one in the left panel and one in the panel to the right of the fixation panel, a false trial and error decision to the left results in the joystick-controlled mouse being imprisoned (negative feedback); (bottom) moving to the right, a hypothetically correct decision results in yellow background positive feedback. Right: examples of three initial colour-form discriminations on the left and of the shifts on the right, reversal from blue to yellow target, ID-shift from pink (vs. blue) to lilac (vs. turquoise), ED-shift from brown to pyramids as target.

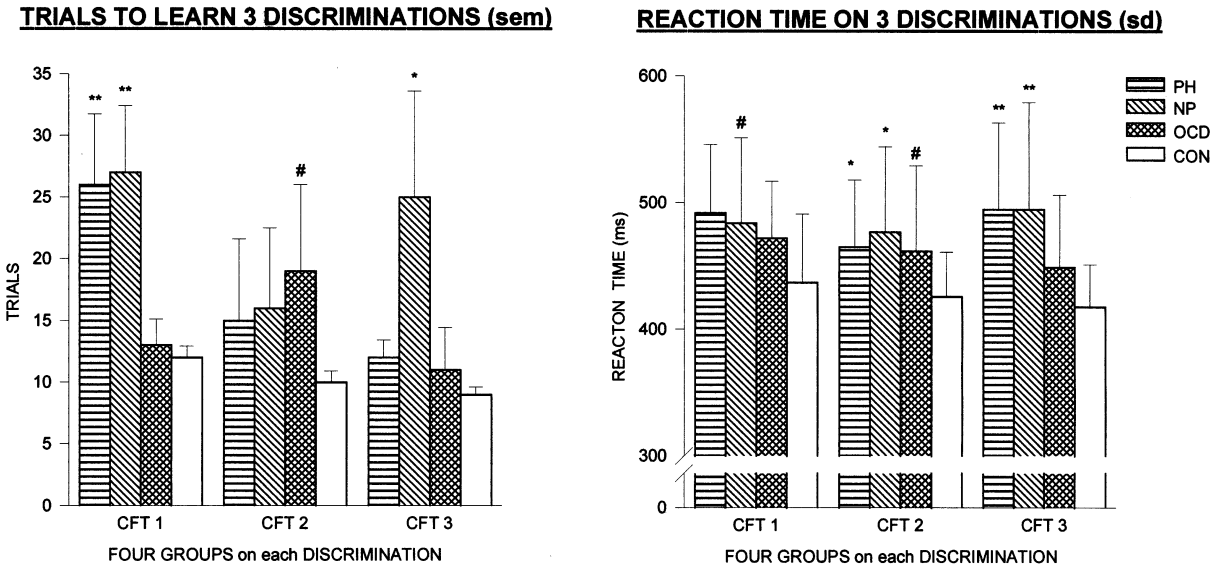

Fig. 2. Left: number of trials needed to learn the first, second and third initial discrimination (CFT1-3). Right: reaction times (RT, ms) on the three initial discriminations by four subject groups. PH, patients with paranoid-hallucinatory schizophrenia; NP, patients with non-paranoid schizophrenia; OCD, patients with obsessive compulsive disorder; CON, healthy control subjects. (# P<0.1, * P<0.05, ** P<0.005).

In a repeated measures analysis (CFT1 -3, Table 2) there was a main group effect, where the SCH group required more trials to acquire the discriminations. There was no effect of session, but a trend for an interaction indicated that SCH patients needed relatively fewer trials on CFT2-3 vs. CFT1 than the comparison groups (i.e. an improvement with practice, Fig. 2, Table 2).

A Friedman ANOVA confirmed the main effects for the four subgroups (Table 2). Controls needed a similar number of trials to learn each task (main session effect, not significant, df 2, *n*= 29, Chi= 2.88, *P*<0.24; but concordance significant, *P*<0.05). NP patients showed the opposite (df 2, *n*=14, Chi=7.3, *P*<0.026; concordance *P*<0.26), requiring relative-ly more trials than controls on the third task (Mann-Whitney *U*=111, *P*=0.017; Fig. 2). In contrast, PH patients needed relatively fewer trials on CFT2 and 3 than controls (*U*=135, *P*= 0.078) and were thus responsible for the improved learning shown by the SCH group as a whole.

3.1.2. *Reaction time* (*RT*).
SCH patients were slower to respond than comparison subjects in CFT1 (significant for SCH and PH; Fig. 2, Table 2). Neither age nor neuroleptic dose correlated with RT (*r*=-0.15, *r*=-0.15, respectively). The use of IQ as a covariate emphasized the significant difference in RT between groups (all subjects, *r*=+0.03; SCH (*n*=27) *r*=+0.296; *P*=0.13; Table 2).

Repeated measures analysis showed a main effect of group with SCH patients showing the longest RTs (Fig. 2). OCD patients also tended to show longer RTs than controls. There was no effect of session but there was a trend for an interaction of group with session (Table 2). Post-hoc analysis confirmed longer RTs with respect to controls on each session for SCH patients (Scheffe *P*< 0.01), especially on the third task (CON< PH or NP, Scheffe *P*<0.0002; Fig. 2).

In summary, controls tended to decrease RT with practice across sessions, but patients, especially the PH and NP groups, did not. SCH patients required more trials to learn the initial discrimination, yet in contrast to controls, the PH group, in particular, improved on subsequent sessions. The learning performance was more variable for NP and OCD patients.

3.2. *Reversal—comparison with non-reversal I/D and E/D shifts*
3.2.1. *Number of trials*
On the reversal task both SCH sub-groups needed more trials to achieve the learning criterion than the comparison groups (Fig. 3, Table 3). However, in contrast to original learning, with IQ as a covariate, the ANCOVA provided a non-significant group comparison (Table 3; *r*(IQ)=-0.37, *n*=70, *P*<0.002). A repeated measures comparison of performance on the 3 shift tasks showed main effects of group, session and their interaction (Table 3). Post-hoc tests con-firmed that (a) the SCH group required the most trials to reach criterion; (b) the reversal task differed from the ID-shift which differed from ED-shift, but reversal did not differ from ED-shift; (c) in the group x session interaction SCH, but not OCD patients, required more trials on the ID-shift/reversal comparison vs. the ED-shift/reversal comparison (Scheffe, all *P*<0.001; Fig. 3).

The non-parametric analysis for the subgroups revealed borderline differ-ences and similarities (i.e. ANOVA vs. Concordance: Table 3, Fig. 3). Controls treated the sessions differently (Fried-man; df 2 *n*=29, Chi=5.7, *P*<0.04; concordance 0.11), while PH and NP patients treated the sessions more similarly (respectively, df 2, *n*=14, Chi= 1.5 and 1.1, *P*>0.47; Concordance *P*<0.05). OCD patients did not show a significant difference or concordance across sessions.

3.2.2. *Reaction time* (*RT*)
SCH (but not OCD) patients showed clearly longer RTs than controls on the initial reversal. Longer RTs were more marked in the PH than the NP subgroup (Table 3, Fig. 3). Age, IQ and medication did not correlate significantly with RT. Repeated measures analysis across the three shift tasks showed a main effect of group and sub-group without a main

Table 3
Summary of results (3 groups, SCH/OCD/CON, and 4 groups, PH/NP/OCD/CON)

Task	ANOVA (*F*-test, 3 groups)			Scheffe *P*			ANOVA (Kruskal-Wallis, 4 groups)				M-W			
	F	df	*P*	CON vs. SCH	OCD vs. SCH	CON vs. OCD	H	df	n	P	PH vs. CON *U*	PH vs. CON *P*	NP vs. CON *U*	NP vs. CON *P*
Trials to acquire post-discrimination shift, shift learning														
CFT1														
Reversa1	4.02,	2, 67	0.022	0.024	ns	ns	8.8	3	70	0.03	102	0.008	118	0.027
Covary IQ	1.0	2, 65	0.386	0.019	ns	ns								
							Friedman (4 groups)							
CFT1-3 (repeated measures)							Chi	df	*n*	*P*				
Group	9.0	2, 67	0.0003	0.0004	ns	ns	5.6	2	70	0.06				
Session	4120	2, 134	0.0001	See text										
Interax	3.4	4, 134	0.01											
Reaction time (*RT*), *shift learning*							ANOVA (*F*-test, 4 groups)				Scheffe *P*			
CFT1														
Reversal	8.8	2, 67	0.0004	0.0004	ns	ns	6.4	3, 66		0.007	0.002		0.07	
Covary IQ	8.4	2, 65	0.0005	0.0007	ns	ns	5.9	3, 64		0.001	0.004		0.07	
CFT1-3 (repeated measures)														
Group	17.5	2, 67	0.0001	0.0001	0.05	0.1	11.8	3, 66		0.0001	0.0001		0.001	
Session	1.3	2, 134	ns				1.6	2, 132		ns				
Interax	0.3	4, 134	ns				0.6	6, 132		ns				

CFT1, session 1, reversal; CFT2, session 2, intra-dimensional shift (ID); CFT3, session 3, extra-dimensional shift (ED); M-W, Mann-Whitney *U*-test; ns, non-significant; *P*, probability; Interax=group x session interaction.

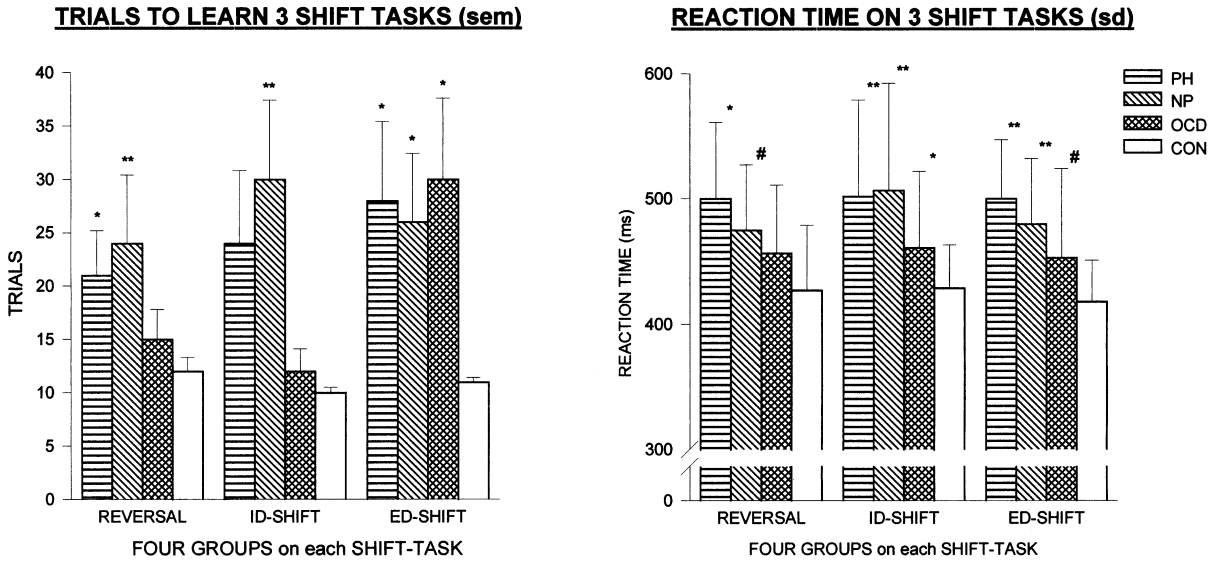

Fig. 3. Left: the number of trials to acquire the reversal (REV), the intra-dimensional shift (I/D) and the extra-dimensional shift (E/D). Right: the reaction times (RT, ms) on the reversal, ID and ED-shift tasks by four subject groups; see Fig. 2 legend (# P<0.1, * P<0.05, ** P<0.005).

effect of session or a group by session interaction (Table 3). The group effect was mostly explained by PH and NP patients exhibiting longer RTs. OCD patients also tended to show longer RTs than controls, but shorter RTs than SCH patients (Table 3, Fig. 3).

In summary, IQ was related to the increase in trials needed by SCH patients to learn the reversal. Nonetheless with respect to reversal they experienced proportionately more difficulty on the ID than ED-shift, where repeated measures analysis suggested that, at least the controls treated the tasks differently. RTs were more (PH\NP) or less (OCD) longer than in controls.

3.3. *Non-reversal shift*

3.3.1. *ID-shift*: *number of trials and RT*

SCH patients needed more trials to learn the ID-shift than either OCD or controls (F(2,67)=8.09, P=0.0007; vs. OCD P=0.034, vs. CON P=0.001, Scheffe). This was confirmed in the sub-group analysis (H (3, n=70) = 8.75, P = 0.033) where the impairment was more marked for the NP than the PH group (vs. CON, NP, U=106.5, P=0.011; PH, U=126.5, P= 0.042; Fig. 3). The comparison with OCD patients approached significance (e.g. PH vs. OCD, U=54, P=0.07).

To test the relationship of reversal to ID-shift performance, the reversal performance was entered as a covariate: this still showed that the SCH group required more trials than the other groups (F(2,66)=5.28, P=0.0009). But repeated measures ANOVA for reversal and the ID-shift did not show a main effect of session. The nonparametric analysis confirmed that for NP (but not PH) patients ID-shift and reversal performances did not differ and were statistically similar (Friedman, Chi (df 1, 14)_P<0.41; Concordance, P=0.05). In contrast, for controls, and to a lesser extent OCD subjects, performance on the ID-shift differed from that on the reversal (respectively, Friedman, Chi (df 1, n=29/13)=4.6/3.6, P<0.03/0.06; Concordance, P=0.15/0.28).

RTs in SCH patients were longer than in controls and tended to be longer than in OCD patients even after covarying for RT in the reversal session (F(2,66)= 4.12, P=0.021; vs. CON P<0.0001, vs. OCD P=0.07 Scheffe; Fig. 3). This was confirmed for both PH and NP subgroups (P<0.003).

In summary, SCH patients needed more trials to learn the ID-shift than other subjects. This difference was more marked in the NP group and was related to their problems in acquiring the reversal. Controls did not show a relationship between ID and reversal shift performance: they treated the tasks differently. This and the lack of concordance

between tasks implies that the ID-shift deficit in PH patients had a different basis to that in the reversal (contrast ED-shift, below).

3.3.2. *ED-shift*: *number of trials and RT*
Controls needed fewer trials to learn the ED-shift than patients (F (2,67)=6.5, P= 0.0026; vs. SCH, P=0.01, vs. OCD P= 0.02, Scheffe; Fig. 3). This was con-firmed for the subgroups (H(3,n=70) =10.9, P=0.012) where PH patients required marginally more (U=131.5, P=0.06), and the NP and OCD groups many more trials than controls (U=105, P=0.01; U=88.5, P=0.005, respectively).

Using the number of trials for reversal as a covariate did not materially alter the result (F(2,66)=8.00, P=0.0008). A repeated measures analysis for reversal and ED-shift sessions confirmed the main effect of group but did not show a clear effect of task (F (1, 67) = 2.81, P = 0.1). In the sub-group analysis, there were no significant differences: all groups showed significant concordance between sessions (Chi = 0.04–0.69, P = 0.84–0.41; Concordance, P = 0.05(NP)–0.001(CON)).

RTs were longer for the SCH than for the controls (F (2, 67) = 15.6, P < 0.0001; Fig. 3): this was significant for both PH and NP subgroups (but not for OCD patients) even after covarying for RTs on the reversal session (Scheffe, vs. CON, P = 0.002 and P = 0.001, respectively).

In summary, ED-shift performance appeared to have some similarity to that on reversal for all groups. Both SCH sub-groups and the OCD patients needed more trials to achieve criterion than controls. For OCD patients impaired acquisition of the ED-shift was a novel finding.

3.4. *Correlations of non-reversal shift performance with conditioned blocking* (*CB*)
Was learning about the added stimulus in the CB task [40] related to non-reversal shift abilities? It is useful to recall, that the controls treated the 3 shift tasks differently, that for PH and NP patients slow acquisition of the ED-shift (and slow ID-shift learning in the NP group) related to slow reversal learning and OCD patients had difficulty with the ED-shift.

Standard regressions on the ranked performance for the three shift-tasks (trials) and two CB latency measures (1- and 3-test-trials) produced no significant results pertaining to group. However, as concordance between CB and the shift measures were seen for the SCH but not the comparison groups (data not shown), correlations for the subgroups were also examined. Twenty four comparisons between these 5 measures produced one significant and one trend correlation (NP: 1 trial CB vs. ID r=0.5, P=0.09; 3 trial CB vs. reversal r=0.66, P=0.019). These values may have arisen by chance. But, while all NP group correlation coefficients were positive (e.g. for ID r=+0.3 to +0.5), for the PH group they were negative (e.g. for ID r=-0.25 to -0.4: cf. PH:NP, ED r=+0.07 to +0.09). Thus, the PH patients who showed the clearest CB were those who needed fewer trials to learn the ID-shift: this is consistent with the controls for whom the ID-shift was the easiest of the three shifts. For NP patients the opposite tendency was seen, namely those who learned about the added stimulus in the CB task needed fewer trials to learn the ID-shift.

In summary, in the comparison groups CB and ID-shift performance did not correlate, as was expected from the theoretical back-ground. This may be attributable to a ceiling effect where controls required very few trials to learn the shift. However, NP patients who showed poor CB tended to be the ones who were more capable on the ID-shift: the more difficulty they had to shift within their attention set, the better they were at blocking out superfluous information.

3.5. *Perseverative errors*, *stimulus-choice and response sequences*
3.5.1. *Error and choice*
At the onset of the reversal PH and NP patients made more errors, but there was only a trend for PH patients to show more ‘perseverative’ errors than the other groups (Table 4, left). What was the cognitive response to reinforcement/ non-reinforcement? Were choices repeated (win/lose-stay) or was another

Table 4

Total and perseverative errors on the reversal task and percentage of correct choices (win-stay, lose-shift) and incorrect choices (errors: win-shift, lose-stay) across all tasks

	Reversal		Correct		Incorrect	
	Total errors	Perseverative errors	Win-stay	Lose-shift	Win-shift	Lose-stay
PH (*n*_14)	9.6[a] (2.2)	3.4[#] (1.1)	31.6[3] (6.9)	36.03 (4.5)	8.0 (3.4)	24.0[2] (4.9)
NP (*n*_14)	11.6[a] (4.2)	2.2 (0.8)	38.9[3] (8.1)	26.81 (5.5)	18.8[1] (3.6)	15.5 (3.8)
OCD (*n*_13)	5.2 (1.6)	1.6 (0.5)	48.6[1] (10.3)	28.61 (6.8)	9.6 (4.3)	13.2 (3.6)
CON (*n*_29)	4.1 (0.8)	1.0 (0.2)	80.1 (5.0)	10.4 (2.7)	4.6 (2.0)	4.9 (2.2)

See text: (right) vs. controls, Scheffe test, [1] $P<0.05$, [2] $P<0.01$, [3]$P<0.001$; (left) # $P=0.10$ (vs. CON, Mann-Whitney, $U=143$). [a] P00.024 (vs. OCD and CON, Kruskal-Wallis (H(3, n=70)=9.44) (S.E.M. in parentheses).

Table 5

Number/length of perseverative response sequences from the mean for colour, form and position sequences in four task-phases

	Median number				Median length			
Session								
Phase:	CFT1 Initial Learning	Reversal	CFT 2 ID-shift	CFT 3 ED-shift	CFT 1 Initial Learning	Reversal	CFT 2 ID-shift	CFT 3 ED-shift
Group								
CON	0.48 (0.11-0.14)	0.52 (0.11-0.22)	0.31 (0.08-0.10)	0.45 (0.09-0.11)	1.34 (0.34-0.40)	1.39 (0.14-0.40)	1.17 (0.24-0.35)	1.38 (0.29-0.41)
OCD	0.31 (0.13-0.29)	0.69 (0.24-0.42)	0.38 (0.10-0.46)	2.38 (0.70-0.85)	1.06 (0.39-1.0)	1.89 (0.38-0.72)	0.82 (0.44-0.54)	2.78 (0.46-0.63)
NP	2.07 (0.52-0.75)	1.71 (0.68-0.86)	1.50 (0.51-0.56)	2.07 (0.54-0.83)	2.39 (0.48-0.51)	1.91 (0.48-0.75)	2.36 (0.56-0.66)	2.86 (0.44-0.87)
PH	1.93 (0.56-0.73)	1.50 (0.29-0.70)	1.50 (0.47-0.72)	2.29 (0.62-0.83)	2.19 (0.56-0.72)	2.26 (0.47-1.1)	2.21 (0.48-0.85)	2.11 (0.42-1.2)

Statistical treatment (ANOVA, see text) included group, task-phase and perceptual dimension: here the medians of the mean data on the three dimensions are shown for each group and these means include individuals with zero values (range of S.E.M. shown in parentheses).

dimension chosen for response (win/ lose-shift). The 4 possible choices, expressed as a percentage of responses in Table 4, differentiated the groups (F (12, 166) = 4.0, P < 0.0002). First, considering correct choices, with respect to controls all 3 patient groups showed half the number of win-stay decisions (i.e. repeat the response just reinforced) but double the number of lose-shift decisions (F (3,66) = 7.5–11.4, P < 0.0002). Second, with respect to incorrect choices, only NP patients shifted response after reinforcement more than controls (win-shift; F(3,66)=4.0, P = 0.011) and only the PH group clearly repeated the non-reinforced response (lose-stay; F(3,66)= 6.2, P<0.0009).

In summary, inappropriate change of the response type after reinforcement was a feature of NP patients; inappropriate perseveration after non-reinforcement was more a feature of PH patients. But all patients failed to show the normal win-stay response as often as the controls.

3.5.2. *Strategies* (*response sequences*)

The number and length of sequences of three or more responses to color form or position (excluding the criterion-achieving sequence)

were also examined as an indicator of a perseverative cognitive style (summary data, Table 5). Taking the initial learning and reversal phases as baseline for the non-reversal shifts, it can be seen that the comparison groups showed a small number of short perseverative sequences. All subjects showed longer colour sequences on reversal (F(5,330)=5.7, P<0.0005) with no group x dimension interaction. On both shift tasks, the two SCH groups showed longer (F(3,66)=3.4, P<0.03), and about three times as many sequences as the others (F(3,66)=6.9, P<0.0005, with no inter-action with task or dimension; Table 5).

Three effects emerge from a detailed comparison of the number of perseverative sequences on the shift tasks (F(27, 170)=2.6, P<0.0002). First, both SCH groups repeated sequences more than controls on all tasks (9/10 dimensional contrasts: F(3,66)=3.2-5.2, P=0.03-0.003). Second, OCD patients showed as many position and form sequences on the ED-shift as the SCH patients, and more than controls (Scheffe P=0.04-0.01). Third, with a repeated measures analysis there was a significant effect of session (F(8,528)=3.9, P<0.002) that reflected more colour sequences on the ED-shift than on the earlier tasks (Scheffe P< 0.05). In other words all groups acquired an attentional set for colour.

The measure of the length of sequences on the shift-tasks confirmed that the PH and NP groups showed more perseveration than controls (F(27,170)=1.7, P=0.022) and differentiated group performance more than the number of sequences. The PH group tended to have longer colour sequences than controls on each task: this held for the NP group only on the ID-shift (P=0.08-0.05, Scheffe). PH and OCD groups tended to show longer form sequences than controls (P=0.09-0.05, Scheffe). Repeated measures analysis (F(8,528)=6.8, P<0.0001) showed that colour-response sequences shortened in the ID-shift (vs. reversal, P<0.02, Scheffe) but increased again in the ED-shift task (Scheffe P<0.001). Sequence length thus provided evidence that the ID-shift was easier than the reversal (Section 1). Also, as the length of colour sequences
increased on the ED-shift, clearly an attention set for colour had been generally acquired.

In summary, all subjects acquired an attentional set for colour: this was more evident in the length than in the number of response sequences to colour. Shorter sequence lengths on the ID-shift suggest that it was easier to acquire than the other tasks. Both SCH groups increased the number and length of perseverative sequences on all tasks with respect to controls. PH were more prone than NP-patients to maintain their attentional set for colour on reversal and ED-shifts, but they were both equally prone to show long sequences on the ID task. OCD patients increased the number rather than the length of a sequence, a pattern of perseveration unique to the ED-shift.

3.6. *Relationship of performance to monoamine metabolic status*

3.6.1. *Group differences and initial learning*

The monoamine data have been presented in detail [38] and related to CB [39, 40]. Subject numbers varied slightly from these reports; but group differences in monoamine utilization were confirmed (F (12, 156) = 2.94, P = 0.001; Table 6). The PH group showed (non-significantly) the highest level of DA activity. The NP group showed clearly more NA and 5-HT activity than the other groups. The OCD group had the highest adrenalin levels but was not distinguished by conventional 5-HT utilization as levels of both 5-HIAA and 5-HT were very high [38].

For initial learning an association between increased NA activity and trials was the only trend across groups (r=-0.25, P=0.04, utilization r=+0.22, P= 0.07, n_67: cf. high activity in NP patients). For controls more trials was associated with higher DA but lower 5-HT utilization (respectively, r=+0.46, P=0.01; r=-0.41, P=0.027), but there was a positive relation for DA activity with stimulus-choice switches (lose-shift, r= +0.36, P<0.05; win-shift, r=+0.42, P<0.02; win-stay r=-0.45, P<0.014). These associations are consistent with the association of DA activity with CB [39, 40].

3.6.2. *Monoamine acti6ity and shift-performance by group*

OCD patients needed many trials to learn the ED-shift and this was positively associated with DA utilization (r=+0.59, P=0.056); but increases of 5-HT vs. DA metabolism related to improved

performance (HVA/5HIAA, r = +0.71, P = 0.014, n=11). 5-HT activity was also important for stimulus choice, being associated with fewer lose-stay errors (r=-0.65, P=0.03), where a build up of the parent amine correlated with more win-shift and lose-stay errors (both, r=+0.72, P=0.01).

Table 6
Level of adrenalin and of the activity (utilization) of dopamine (DA), noradrenaline (NA) and serotonin (5-HT) in 24 h urine samples from 4 subject groups (S.E.M. in italics)

	Adrenalin	HVA/DA	MHPG/NA	5-HIAA/5-HT
PH (n, 13)	3.5 (0.9)	13.8 (3.1)	60.6 (17.7)	29.3 (5.4)
NP (n, 14)	3.7 (0.7)	11.4 (2.0)	112.2[2] (36.9)	34.5[1] (7.3)
OCD (n, 11)	5.8[3] (1.3)	10.3 (1.2)	34.5 (6.1)	17.1[a] (3.3)
CON (n, 29)	2.5 (0.3)	9.2 (0.8)	42.6 (3.9)	16.9 (2.7)

Utilization ratios, metabolite to monoamine levels; adrenalin levels in ng/mg creatinine/m^2 body area (volume corrected 24 h samples). Newman-Keuls contrasts: ***1*** P<0.025 (vs. CON, P<0.07 vs. OCD); ***2*** P<0.016 (vs. CON, P<0.08 vs. OCD and PH); 3 P<0.007 (vs. CON, P<0.07 vs. NP); ***a*** 5-HT levels high vs. other groups.

For PH patients the high level of DA activity was positively associated with the number of trials to reversal (r=+0.58, P=0.037). Both DA and 5-HT utilization tended to be negatively related with the number of trials needed for the ID-shift (r=-0.49, P=0.09; r=-0.58, P=0.039, n=13, respectively; Fig. 4). For stimulus-choice, increasing NA activity correlated with correct win-stay choices (r=+0.63, P<0.02) but inversely with correct lose-shift choices (r=-0.78, P<0.002).

For NP (and PH) patients, initial learning was not associated with monoamine activity. But, in NP (not PH) patients, increasing 5-HT activity correlated with trials on the ID-shift (r=+0.80, P=0.001; Fig. 4). For the ED-shift increasing catecholamine metabolism, recorded as high, was negatively associated with the number of trials (HVA, r=-0.57, P=0.03; MHPG, r=-0.66, P=0.01). Indeed, NA utilization was negatively related with the incorrect lose-stay stimulus choice (r=-0.53 P<0.05). Reductions of this type of error when NA metabolism was high may have contributed to it occurring less frequently than in PH patients (Tables 4 and 6). However, high levels of 5-HT activity correlated negatively with the incidence of correct win-stay choices (r=-0.5, P=0.08).

To summarise, in general, high levels of DA and NA activity had a negative and of 5-HT a positive association with initial learning performance. For OCD patients impaired ED-shift may relate to a proportionately greater increase of DA metabolism over that of 5-HT metabolism. In contrast, in NP patients poor ED-shift related to low DA and NA metabolism and poor ID-shift to increased 5-HT metabolism. The contrast with PH patients was that increased levels of 5-HT metabolism had a negative association with trials on the ID-shift, as did increased levels of DA metabolism, despite the association of increased DA metabolism with poorer reversal performance.

4. Discussion

4.1. *Learning* (*Sections* 3.1, 3.2 *and* 3.3)

Normal subjects learned the 3 tasks rapidly and decreased their RT with practice. A floor effect probably prevented them requiring fewer trials with practice. In contrast both SCH groups required more trials, but improved with practice. But, they were unable to speed up RTs with practice, supporting the contention that such an indicator of the speed of information processing is trait related [57] and not very sensitive to the nature or difficulty of the tasks. By comparison, the measures for OCD patients varied considerably, but their RT did decrease with practice. An analysis of the variance in controls' performance between tasks indicated that they responded differently to each. In this, the ID-shift was unlike the other two tasks but the ED-shift resembled the reversal. Among the study groups the NP patients alone responded similarly to the tasks implying that they had a nonspecific problem with learning. This problem was especially marked for the ID-shift reputed to reflect attentional abilities (Section 1). Impaired learning of the ED-shift found here was expected from reports of problems of patients with schizophrenia on a similar task and on card-sorting tasks with similar demands [12, 30]. Less expected was a marked impairment for the OCD group specific to the ED-shift. There is limited support in the literature for executive (frontal) deficits in OCD [7], but there are tomographic reports of changes in frontal,

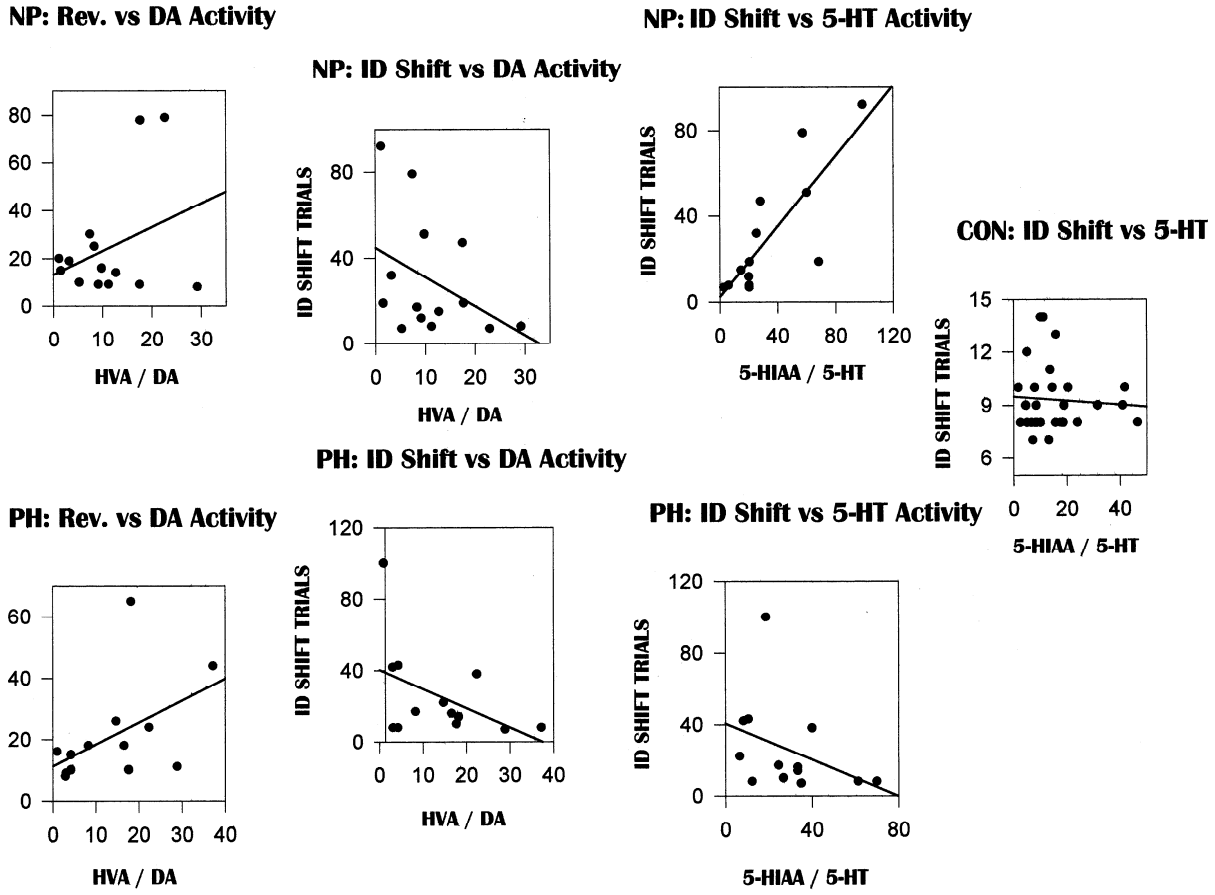

Fig. 4. Top row, for NP, bottom row, for PH patients: a comparison of first order regressions between trials to learn the reversal (left) and ID-shift (mid-left) and DA activity are similar between groups; for ID-shift and 5-HT activity (mid-right) the PH and NP groups differ: for comparison the absence of a relationship in controls (far-right, significance levels in text). (Increased DA activity relates to delayed reversal but facilitated ID-shift in both groups. Increased 5-HT activity relates to delayed shift in NP but not in PH or controls (CON). (cf. Pearson rho for HVA:MHPG with CB (trials 1–3): CON +0.41, OCD +0.61, PH +0.12, NP -0.85, $P<0.05$, not PH).

especially orbito-frontal, regions likely to be involved in mediating these abilities [14].

4.2. *Conditioned blocking* (*CB*; *Section* 3.4)

Was there a relationship between shift and CB measures of learned inattention? (Here it should be recalled that 'normal' CB indicates delayed learning about the added stimulus). We reported that while the OCD and control groups showed normal CB, the SCH did not [40]. The NP group was consistently impaired across CB test trials, while the PH group was only transiently impaired on the first trial. The concordance for the shift with the CB-tasks for both SCH groups points to the maintenance of the cognitive style on both tasks. The positive association for CB and ID-shift in NP patients implies that the more they learned about the added stimulus (impaired CB) the fewer trials they needed to acquire the ID-shift. Hence 'good' learning on both tasks correlated even though the attentional strategy leading to this may not be a 'normal' adaptive one. PH patients provided the mirror image of this. In terms of task demands the better their CB index, the faster they made the ID-shift. This illustrates a difference in cognitive style between PH and NP patients on the ID-shift and CB tasks. The absence of the predicted relationship between the 2 tasks for controls may be attributed to the ease of the discriminations not allowing a wide enough distribution of the data to allow the detection of differential abilities.

4.3. *Response sequences and set* (*Section* 3.5)

As the primary measures of the number of learning trials and RT only subtly reflected the variance of responding within groups to the different sorts of shift, several behavioural measures of cognitive style were studied. These included stimulus selection strategies as

reflected by sequences of responses to a given stimulus type, which will now be discussed, and decisions to repeat or switch between stimulus types (Section 4.4).

The decision to start each task with colour discrimination was successful in inducing an attentional set for colour, as measured by the number and length of response sequences to colour. Accordingly, for the comparison groups the ID-shift was easier to learn than the other shifts. But, as it is widely reported that schizophrenics have a limited ability to maintain attention set [53], that this is more evident in acutely ill young patients [33] as tested here, and it may be related to structural and functional problems in the parahippocampal and superior temporal gyrus [32], it is important to note that our patient groups acquired such sets. This could imply that the temporal lobe was functioning normally in our patients or that its function is not strongly implicated in learned inattention, as has been suggested in a study of epileptic patients [18].

Further analysis of response sequences to one of the stimulus dimensions revealed that OCD patients differed from controls only on the ED-shift where they showed more (but not longer) sequences. This points to a frontal executive impairment (see above) but that its nature differed from the SCH groups. In contrast, SCH patients showed more and, in particular, longer perseverative sequences, which, in the shift-tasks, was more evident in PH than NP patients. This recalls the distinction between two sorts of perseveration described by Abbruzzese et al. [1] using measures of fluency, card and block sorting. While their schizophrenics showed perseverative errors, the OCD patients had difficulty establishing and maintaining the category or set.

Here perseveration with colour sequences, seen in the SCH group on each shift-task, was mainly found in NP patients on the ID-shift. This is import-ant as perseveration on card-sorting tasks has often been reported to be more severe in patients with predominantly negative symptoms comparable with our NP group [5] and been related to decreased frontal blood flow [50]. However, there are reports of perseveration in patients with marked positive symptoms [46]. Nonetheless, even though the ID-shift was always presented before the ED-shift, the sequence of conditions in which Elliott et al. [12] found the more exaggerated persev-eration in patients with schizophrenia, a marked increase of perseverative responding on the ED-shift did not reach the levels these authors have reported for patients with frontal damage or Parkinsonism [44].

4.4. *Errors and choices* (*Section* 3.5)

The reversal-shift induced SCH patients to make more errors than the comparison groups, with perseverative errors slightly predominant in the PH group. As learned inattention and non-reversal shift are studied with associative learning performance, we decided to analyse errors in terms of stimulus-choice strategies to see if elementary rules (e.g. win-stay, lose-shift) used in animal and human problem solving applied ([10,34]).

Our patients, compared with controls, had a decreased sensitivity to the positively reinforced consequence (fewer win-stay decisions) and an increased sensitivity to the absence of reinforcement (more lose-shift decisions) in common. As errors generally increased, the latter should not be viewed as an automatic consequence of the former. The type of error that separated the PH and NP groups recalls Gray's [16] description of behavioural inhibitory and approach systems. NP patients showed more win-shift errors which is consistent with their being less sensitive to reward (approach system). But, this is not consistent with the increase of lose-shift decisions. PH patients showed more lose-stay decisions implying that they were less sensitive to reward omission (impaired inhibitory system). But, this is not consistent with their appearing to be less sensitive to reward (fewer win-stay decisions). An interpretation in terms of approach to reinforcement may be premature. the Instead we prefer a view that describes processing strategy (attention: next paragraph). (The basis for this lies in the status of neurotransmitter activity which in this study is

influenced by medication and psycho-pathology, Section 4.5).

The differential performance of the SCH groups on the shift tasks is viewed as follows. As predicted in the introduction, performance in normal subjects (and PH patients) on the ID-shift did not relate clearly to that on the reversal task. The attentional set for colour may have helped controls to solve the ID-shift more quickly than the reversal. But, PH patients had difficulty to apply this strategy: their use of controlled processing throughout learning made it difficult to disengage from plausible, but non-target alternatives (perseverative sequences and more lose-stay choices). The difficulty for NP patients was in fundamentally learning the reinforcement association of the new stimulus; serial automatic pro-cessing of all information in each task led naturally to more learning trials, without the differential perseverative response pattern of PH patients (i.e. more win-shift choices). NP patients do not have enough channels or capacity available to do this efficiently and hence they learn about the added stimulus in the CB task [19, 40]. The relation between ID and CB performance in NP patients was predicted, but the expected relative decrease of impairment in PH patients on ED-shift was not found. This may reflect the young age and short illness duration of our patients compared to those usually studied.

4.5. *Relationships of monoamine metabolism to performance* (3.6)

In controls, poorer initial learning was associated with higher levels of catecholamine activity and faster learning with increases of 5-HT activity. DA metabolism correlated positively with shift and negatively with stay-choices in controls, facilitating reversal. While the ED-shift impairment of OCD patients correlated with DA activity, a relative increase of 5- HT (over DA) activity was associated with improvement. Indeed, decreases in the incidence of lose-stay errors correlated with increased 5-HT activity.

For PH patients high levels of DA activity were associated with a delayed reversal, but high levels of DA and 5-HT activity were related to a more rapid ID-shift. Intriguingly, increases of win-stay and decreases of lose-shift were associated with NA metabolism. In contrast, for NP patients poor ID performance (and increased lose-stay errors) correlated with the high levels of 5-HT metabolism. Unlike the others, ED- performance correlated negatively with their high level of catecholamine metabolism.

We posited that background mono-amine activity levels indicate the pre-dominant mode of particular information-processing mechanisms and these are reflected in correlations with the performance of tasks with different requirements. Thus, DA activity increases the chance of a switch between the inputs to a brain region that are competing for control of the output: NA activity tunes the relative influence of the combined inputs on the output: 5-HT activity exerts a volume control on the output via a direct inhibitory or indirect disinhibitory influence [35, 36, 38].

DA activity would be expected to play a role in shift performance, not only on the basis of the extensive animal work [35, 36], but considering that L-DOPA treatment is helpful on these types of task in Parkinson's patients [11, 24, 44]. Indeed, Parkinson's patients have been described as developing fewer hypotheses for task solution resulting in fewer lose-shift decisions [6]. Here we could report the opposite effect in controls, who showed a positive correlation for both win- and lose shift decisions with DA activity and a negative relationship with lose-stay. At the start of learning hypothesis-switching may be an advantage, but it soon interferes with the maintenance of the correct choice (trials correlate with DA activity). Further, volume control from 5-HT activity is important for concentrating on the salient stimulus (negative correlation with trials). This was supported by the relationship of the DA and 5-HT metabolites in OCD patients who had difficulty with the ED-shift. The switching hypothesis also accounts for the difficulty patients had in maintaining a win-stay and the relative ease with which they could adopt a lose-shift strategy.

NA activity had a mild influence across subjects befitting its role in tuning that would

be expressed in a large number of brain regions. Nonetheless relatively high levels were associated with improved ED-shift performance (NP) and prevalence of the lose-shift decision (PH and NP). The contrast for the same data with CB performance is instructive. For controls there was a marked positive relation of both DA activity and its relation to NA activity with CB: for NP patients the HVA/MHPG measure showed an even more marked negative relation-ship to CB. This brings the essential difference between the tasks into focus. In CB it is normal to switch away from the influence of the distracting newly added stimulus; tuning, which is biased to novel stimuli, has a negative influence. In the shift tasks the difficulty for SCH patients lay not so much with an initial alternative choice, as in CB, but in the maintenance of this choice if correct. Hence there was a positive relationship of NA activity with PH patients on win-stay and lose-shift decisions and NP patients on the lose-shift, especially the ED-shift.

Mesolimbic 5-HT activity facilitates attention-related septo-hippocampal theta activity [36] and 'disrupts the disruption' associated with a soft audit-ory pulse just before a loud startle-eliciting noise (prepulse inhibition [45]). These effects are subsumed under the rubric of volume control that assists the processing of salient stimuli, even if this may not be adaptive, as in the case of sensory gating. Thus, as reported above and predicted from a role in volume-control, in normal bounds 5-HT activity is positively associated with learning. But, too much activity, and high levels of metabolism were evident in NP and OCD patients, would be expected to disrupt adaptive performance by 'turning up the volume' or facilitating choice of the inappropriate stimulus. Consistent with this view, we found a non-adaptive correlation for NP patients on the ID- shift but helpful relations for OCD patients on the incidence of lose-stay choices and learning about stimuli during the CB test phase. This interpretation is also consistent with effects in latent inhibition [20]: thus, if 5-HT activity is associated with volume-control for salient stimuli, 5-HT agonists would be expected to exaggerate further the lack of salience of contextual cues and hence facilitate learning about a new consequence for a familiar cue ('disrupted latent inhibition').

What parts of the brain are implicated in these functions and dysfunctions? Studies of sequential behaviour and decision-making in animals have shown that damage to the prefrontal and suprarhinal areas introduce errors into cue utilization and the development of task-solving response-sequences, as here [31]. These areas receive much mono-aminergic innervation that influence working memory formation, crucial to task solution [62]. Changes of prefrontal activation with state, cognitive demands or pharmacological challenge in patients with schizophrenia [9] and orbital frontal areas of OCD patients have been reported [58]. There is a vast input from the frontal lobe to the nodal point of the entorhinal cortex, also innervated by midbrain monoaminergic systems [37]. The interactions of this and the other major afferent node, the septo-accumbens complex, with the comparator role of the hippocampus [15] control decision making on stimulus input. There is abundant evidence that monoamine activity in these nodes is involved in mediating switching activity [59] and latent inhibition [61] and that the balance between mesocortical and mesolimbic DA activity is important for CB in animals [41]. Indeed, it has been extensively argued that dysfunction in these nodes may make a marked contribution to impaired information processing during acute episodes of schizophrenia [17].

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