

Psychomotor impairment and cognitive disturbances induced by neuroleptics

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Reviews of the literature have failed to demonstrate any consistent effects of typical or atypical neuroleptics on psychomotor or cognitive function in schizophrenic patients. Better methods and study designs are required, and healthy volunteer studies are necessary to control for variables due to schizophrenic psychopathology. Eye movements are a sensitive, reliable and relatively pure measure of attention and arousal. Two volunteer studies of the effects of single doses of haloperidol (2, 4 and 6 mg), chlorpromazine (50 mg) and remoxipride (100 and 150 mg) on saccadic and smooth pursuit eye movements are described. All drugs impaired both eye movement measures, but the doses used were not clinically equivalent. No available test is yet able to distinguish between benzodiazepines and neuroleptics.

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In spite of the theme of most of the other articles in this symposium, reviews of the literature have in fact shown that it has been remarkably difficult to demonstrate cognitive deficits in schizophrenic patients that can be unequivocally attributed to their neuroleptic treatment. This would appear to be analogous to the situation with electroconvulsive therapy (ECT) and memory, in which memory deficits following ECT are generally not detected in depressed patients, since the illness itself is associated with impairments in memory and the beneficial effects of the treatment outweigh its adverse consequences. Cognitive function in schizophrenia has been conceptualized in 3 different ways:

- attentional (information-processing) deficit as measured by such tests as the continuous performance test (CPT), the span of apprehension test (SAT), the critical flicker fusion threshold (CFFT) or various visual backward masking tests, etc.;
- intellectual impairment as measured by such tests as the Withers & Hinton score, the Wechsler Adult Intelligence Scale (WAIS), proverbs, Paired Associate Learning or the Peabody Picture Vocabulary Test; and
- formal thought disorder, as measured by various thought disorder indices from the WAIS or the Rorschach tests, or "conceptual disorganization" as measured by ratings of psychopathology on the Brief Psychiatric Rating Scale (BPRS).

Clearly these different aspects of cognitive malfunction are interrelated, but the questions remain as to which is primary and on which do neuroleptics principally act? A related but separate question is the extent to which neuroleptics are responsible for negative symptoms. At the present time there can be no clear answer to this question. Crow (1) first described negative symptoms as being "neuroleptic resistant". Other authors have frequently said that negative symptoms are "neuroleptic induced" (2-4). This is controversial, since others have maintained that negative symptoms are at least partially "neuroleptic responsive" (5-9). The latter position has also been taken by French psychiatrists, as reviewed elsewhere in this supplement by Lewander and by Colonna. This situation is further complicated by the fact that the net effect of neuroleptics might depend both on the dose used (10) and the particular spectrum of activity of the neuroleptic used.

Review of studies in schizophrenic patients

The literature on the effects of neuroleptics on cognition in schizophrenic patients has been the subject of several reviews from different points of view.

Heaton & Crowley (11) reviewed 12 studies in schizophrenic patients from the point of view of the neuropsychologist. They thought that 3 attributes of these drugs, sedation, anticholinergic effect and extrapyramidal effects, might be expected to lead to impaired test performance. However, they concluded

that few significant changes occurred once patients were stabilized on neuroleptics and that, on balance, these drugs enhance performance on tests of attention.

Medalia et al. (12) classified their review according to different neuropsychological tests. They found that there were consistent reports of impaired memory and fine motor coordination, probably related to muscarinic and dopamine receptor antagonism, respectively. They also found that some studies reported impaired planning, but that tests of language, intelligence and attention (including the Halstead-Reitan test battery) gave equivocal results.

Spohn & Strauss (13) estimated that the relevant literature in this field exceeded 400 published reports. They extensively reviewed 109 of these and noted that the great variability in experimental design led to difficulties in interpretation of the literature. They concluded that neuroleptic treatment was associated with normalization of disordered thinking and of attention and information-processing dysfunction but that no direct cause-and-effect relationship between these could be inferred. They also concluded that some neuropsychological and psychophysiological measures were unaffected by treatment and may therefore be trait markers, such as the reaction time crossover effect, the orientating-response non-responding, and impaired smooth pursuit eye movements.

Cassens et al. (14) also reviewed this literature and, like Medalia et al. (12), classified the studies according to individual test results and provided several very useful tables. They contrasted the effects of acute with chronic neuroleptic drug treatment in chronic schizophrenic patients and concluded that chronic dosing was associated with improved performance on both sustained attention and visuomotor function and that there were no significant residual psychomotor impairments.

King (15) also found great variability in the literature and, of 30 early studies in schizophrenic patients, 10 reported no change or variable effects, 6 reported impairments and 14 found improvements in at least some tests. The tests that seemed to be most sensitive to neuroleptics were paced (had to be performed within a certain fixed time schedule) such as the CPT, the SAT, a rapid information-processing test and various visual backward masking tests. Such tests as the WAIS, the digit symbol substitution test (DSST), the Wisconsin card sorting test (WCST) and the Stroop test were carried out at the subject's own pace and tended to be insensitive to neuroleptics. However, there were still many inconsistencies, and the CPT was found to be improved by neuroleptics in 4 studies and impaired in 2 studies.

Another important issue is whether attention and thought disorder are interdependent or can vary in-

dependently. Spohn et al. (16) initially believed that the improvement in psychopathology was secondary to improved attention. However, in a subsequent study when they found that the SAT had improved but there had been no change in the thought disorder index, they concluded that the attentional deficit could not be primary (17). The converse findings by Gold & Hurt (18) led them to similar conclusions. They found no change in cognition as measured by the WAIS but improvement in the thought disorder index and therefore concluded that the primary effect was on the clinical state. This problem has also recently been addressed by Goldberg et al. (19), who carried out a range of neuropsychological tests in 15 patients before and 15 months after clozapine treatment. They found that clozapine was associated with a 38% fall in psychopathology as measured by the BPRS and also in the Clinical Global Impression score. However, there was no change in the neuropsychological tests which included the WAIS, the Wechsler memory score, the Trails B test, DSST and WCST. Interestingly enough, they also found that there had been no significant change in the social functioning of their patients as measured by living arrangements and occupation at the end of the trial. Thus it would appear that neuroleptic drugs have a direct effect on psychopathology and minimal effects on cognition and that there is no direct relationship between cognitive or attentional effects and psychopathology. It may be, however, that social functioning is more dependent on the cognitive deficit than on the psychopathology in these patients.

Need for volunteer studies

It is clear that there are a number of confounding variables in studies of patients, such as the difficulties in controlling for the dose and duration of treatment; variables due to intelligence, practice effects and motivation; and the type and severity of the schizophrenic illness itself. Clearly we need a body of sound knowledge of the effects of these drugs in volunteers to establish what are the principal effects of these drugs. When such studies were initially carried out in the 1960s, it was concluded that the principal effects were on sustained attention or vigilance rather than on cognition *per se*. For example, Mirsky & Kornetsky (20) summarized a series of studies in which they demonstrated that, while barbiturates caused substantial impairments on both DSST (a measure of cognition) (33%) and the CPT (a measure of sustained attention or vigilance) (18%), chlorpromazine had little effect on the DSST (9%), but major effects on the CPT (39%). Subsequently, however, this has not been a consistent finding, since given an adequate experimental design (using single doses of chlorpromazine of at least 50 mg, measur-

ing the peak effect at 4 h and using at least 8–12 subjects), then chlorpromazine can be shown to cause impairments on all conventional tests whether paced or unpaced, such as the CPT, DSST, CFFT, choice reaction time, letter cancellation and finger-tapping tests. Studies with haloperidol have also shown very similar findings provided doses of at least 2 mg, and preferably more, are used. These human volunteer studies have been reviewed in more detail elsewhere (21). A number of attempts have been made to find new test strategies that would define the neuroleptic effects more precisely and be more relevant to the psychophysiological basis of schizophrenia. Many of these have involved putative “frontal lobe” tests but, in fact, none of these is likely to be selective for frontal lobe function (22). Moreover, those who have looked for an effect on the shifting of attention have reported opposite findings (23, 24).

Studies of eye movements

We have been interested in a number of measures of different eye movements as a way of investigating psychotropic drug effects in general and neuroleptics in particular. We have hypothesized that the eye movements that involve a large degree of attention and voluntary control would be more likely to be affected by neuroleptics than those which are involuntary.

Saccadic eye movements (SEM) are the rapid conjugate shifting of the eyes that occur when a subject immediately shifts attention from one target to another. These are the most rapid movements of which the body is capable and generate eye speeds of up to 600° per second. Thus, although they are initiated by a voluntary process, once started they are involuntary and their velocity cannot be altered by voluntary effort. The basic neurophysiology is well described and is localized as a pulse generator in the paramedian pontine reticular formation of the brain stem (25). They are very sensitive to drowsiness and to the sedative effects of a range of central depressant drugs such as alcohol, benzodiazepines, barbiturates and opiates (26, 27). They have thus proved to be a fairly selective measure of sedation uncontaminated by cognitive effects.

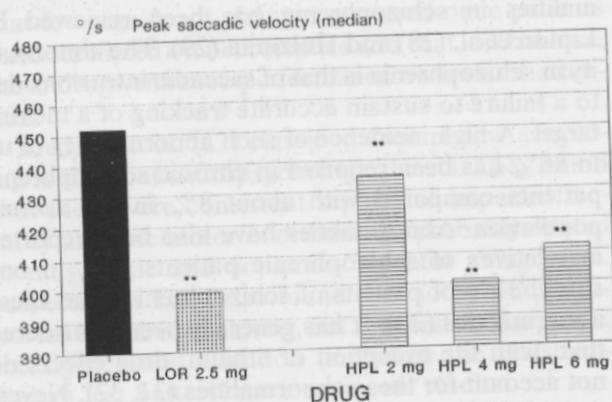
Smooth pursuit eye movements (SPEM) on the other hand, occur when a subject is following a slowly moving target that has to be kept focused on the retina. They are thus a much more complex movement and involve a number of higher centres in the brain such as the frontal eye fields, the striatum, the substantia nigra, the thalamus and the superior colliculus. They are impaired by fatigue, poor attention and lesions of the visual pathways and in schizophrenia. A substantial literature on SPEM abnor-

malities in schizophrenia has been reviewed by Lipton et al. (28) and Holzman (29). The abnormality in schizophrenia is that of saccadic intrusions due to a failure to sustain accurate tracking of a moving target. A high incidence of such abnormalities of up to 86% has been reported in chronic schizophrenic patients compared with about 8% in the normal population. Abnormalities have also been reported in relatives of schizophrenic patients and, in one study, 34% of parents of schizophrenics had these abnormalities (30). It has generally been considered that, with the exception of lithium, drug effects do not account for these abnormalities (31, 32). Nevertheless, caffeine (31), tobacco (33) and benzodiazepines (34) as well as lithium (35) have all been shown to impair smooth pursuit tracking in healthy volunteers.

We have been using the Cardiff System for the Generation and Analysis of Saccades (CSGAAS) (27) to measure both types of eye movements. This employs a smoothed electro-oculogram signal that is filtered, amplified and digitized and yields a number of variables. For saccades, latency, duration, accuracy, velocity, acceleration and deceleration of saccades can be computed. For SPEM, position error and velocity error can be calculated, and we have recently developed an objective measure for saccadic intrusions. Using this system we have carried out a number of studies with neuroleptics in healthy volunteers (36–38). These studies found that peak saccadic velocity was the most sensitive saccadic measure of drug effects and was sensitive to single doses of temazepam (20 mg), lorazepam (2.5 mg), promethazine (50 mg) and chlorpromazine (50 mg and 100 mg). Haloperidol (5 mg), however, was not detected in these earlier studies (36). To date, no single psychomotor or cognitive test has been able to distinguish between drugs with an antipsychotic effect from those with nonspecific sedative properties (21). The preliminary findings from two of our more recent studies involving the latest edition of the CSGAAS system and incorporating measures of SPEM are reported below.

Effects of haloperidol on the visual search, eye movements and psychomotor performance

Calvert & Troscianko (39) have shown that patients with Parkinson's disease had impaired parallel processing on a visual search task. This incorporated the simple task of detecting a vertical bar in the presence of varying numbers of distracting horizontal bars. The processing time did not vary according to the number of distractors in control subjects, but was significantly impaired with an increasing number of distractors in patients with Parkinson's disease. This was interpreted as showing that the

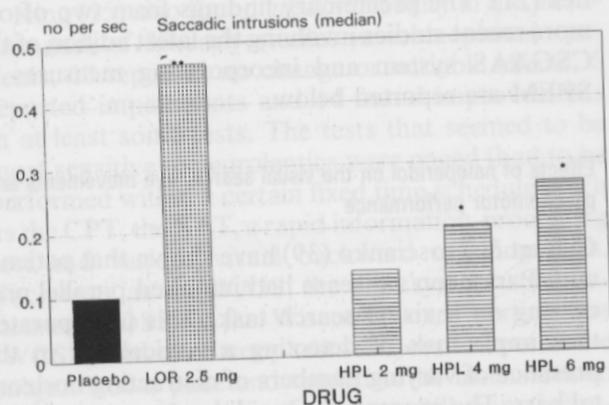


** $p < 0.01$

Fig. 1. Histograms of the effect of three single doses of haloperidol, lorazepam and placebo on peak saccadic velocity in 15 healthy male volunteers.

patients substituted a form of serial processing for parallel processing in this task. The principal aim of this study was to see whether single doses of haloperidol would replicate this effect in healthy volunteers. We also looked for evidence of a dose-dependent effect on both SEM and SPEM. Fifteen healthy male volunteers received haloperidol (2, 4 and 6 mg), lorazepam (2.5 mg) and placebo 1 week apart in a double-blind balanced Latin-square design. SEM, SPEM, DSST and visual analogue ratings of subjective feelings were measured at baseline and at 2, 4 and 6 h of drug administration. The visual search and continuous attention tasks (CAT) were assessed at baseline and 4 h.

None of the drugs were found to impair parallel search; these results will be reported in detail elsewhere. All the drugs, however, impaired peak saccadic velocity (Fig. 1) and increased the number of



* $p < 0.05$ ** $p < 0.01$

Fig. 2. Histograms of the effect of 3 single doses of haloperidol, lorazepam and placebo on smooth pursuit eye tracking, showing number of saccadic intrusions per second, in 15 healthy male volunteers.

Table 1. Incidence of dysphoria and akathisia after haloperidol in 15 volunteers

	Nil	Mild	Moderate	Severe	Very severe	% with ADR
2 mg	15	—	—	—	—	—
4 mg	6	6	2	1	—	60
6 mg	3	3	6	2	1	80

saccadic intrusions during the smooth pursuit (Fig. 2). Lorazepam had a greater effect than any of the doses of haloperidol. The effect of haloperidol on SEM plateaued at 4 mg, but a clearer dose-dependent effect was noted in its effect on SPEM. The incidence of reported adverse effects in this study is also shown in Table 1. Volunteers reported a high incidence of subjective dysphoria and akathisia with 4 and 6 mg of haloperidol but not with 2 mg. This effect was described as tension, irritability and restlessness. It is remarkable that the dose at which this effect is first noticed is very similar to the dose at which the "neuroleptic threshold" was found in patients by McEvoy et al. (40). He found the mean of this was 3.7 mg and suggests that the tolerance for acute doses of neuroleptics, at least, is no different in patients than in volunteers.

Effects of remoxipride and chlorpromazine on eye movements and psychomotor performance

Remoxipride (immediate release, 100 mg), remoxipride (controlled release, 150 mg), chlorpromazine (50 mg), lorazepam (2 mg) and placebo were given 1 week apart in a randomized crossover design to 15 healthy male volunteers. SEM, SPEM, CFST, CAT (41), the DSST, an automated symbol digit substitution test and 10 visual analogue rating scales were measured at baseline and at 1.5, 3.0, 4.5, 6.0, 7.5 and 9.0 h post-dosing. The results of this study will be reported in detail elsewhere, but a summary of the effects found on peak saccadic velocity is shown in Table 2. All drugs significantly impaired peak saccadic velocity, with the maximum effect being caused by lorazepam followed closely by chlorpromazine. The 2 doses of remoxipride caused a smaller effect.

Table 2. Remoxipride study: peak saccadic velocities

	Remoxipride				
	PL	CR	IR	CPZ	LZ
Area under the curve (degrees \cdot s $^{-1}$ \cdot h $^{-1}$; SE=46.2)	4120	3950*	3986*	3928**	3693**
Maximum impairment (degrees \cdot s $^{-1}$; SE=8.63)	437	404**	416	404**	365**

* $P < 0.05$; ** $P < 0.01$

The importance of this finding is that the remoxipride was being used in clinically effective doses but the chlorpromazine was about one sixth of the minimum effective daily dose. This clearly shows remoxipride to be substantially less sedative than chlorpromazine, and in so far as a number of the cognitive effects are secondary to sedation it can be expected to have fewer adverse cognitive effects as well.

Conclusion

- The present system of measurement of both saccadic and smooth pursuit eye movements is sensitive to a wide range of centrally acting drugs, including relatively nonsedative neuroleptics such as haloperidol or remoxipride.
- Since remoxipride is a selective dopamine D₂ antagonist, these results suggest that eye movements are sensitive to any change in central neurotransmitter function, including dopamine receptor blockade.
- How changes in these systems are correlated with the clinical profile of adverse drug effects needs to be explored by further studies involving both patients and healthy volunteers.
- The role of concurrent medication in contributing to smooth pursuit eye movement abnormalities in schizophrenic patients needs to be re-evaluated. Although it is often cited that these abnormalities were noted before the neuroleptic era, it is clear that any sedative drug such as barbiturates could have had the same effects as lorazepam noted in the above studies.
- Neuroleptics did not have differential effects on saccadic eye movements and smooth pursuit eye movements.
- None of our tests distinguish antipsychotic drugs from benzodiazepines. Thus, at present, it would appear that the only observable difference between the effects of these 2 groups of drugs in healthy volunteers is that the benzodiazepines cause pleasant sedation, whereas the neuroleptics cause unpleasant sedation.

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