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Haloperidol-Induced Changes in Blink Rates Correlate with Changes in BPRS Score

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Summary: Spontaneous eye blink rates, psychiatric symptoms and response to neuroleptic medication may all be mediated by dopamine. Fixed doses of haloperidol, a dopamine blocking agent, were administered for six weeks to 17 chronic schizophrenic patients who had been previously withdrawn from all medications. The change in blink rates caused by haloperidol corresponded to a change in the thought disturbance syndrome which measures positive symptoms ($r = .48$, $P < .05$). The relationship was particularly clear in patients with normal cerebral ventricles ($r = .74$, $P < .01$).

The dopamine hypothesis of schizophrenia (Carlsson and Lindqvist, 1963) attributes the etiology of the illness to increased dopamine activity in the central nervous system and the efficacy of neuroleptic medication to dopamine blockade. The substantial group of chronic schizophrenic patients with large cerebral ventricles as measured by computerized axial tomography (CT) scan has been identified as a subgroup that does not seem to fit the dopamine hypothesis. Patients in this group have been characterized by the prominence of negative symptoms (anergia, negativism, blunted affect) (Johnstone *et al*, 1978a), a poor response to neuroleptic medication (Weinberger *et al*, 1980a), a poor premorbid history (Weinberger *et al*, 1980b), neuropsychological impairments (Johnstone *et al*, 1976; Donnelly *et al*, 1980) and the absence of the inverse correlation between plasma prolactin concentrations and psychiatric abnormality seen in normal ventricle patients (Kleinman *et al*, 1981).

Recent evidence suggests that the spontaneous eye blink rate may be an indicator of central dopamine activity. Blink rates are decreased in Parkinson's disease (Hall, 1945), an illness where there is a decrease in central dopamine activity, and increased in some schizophrenic (Kraeplin, 1919; Stevens, 1978) and Tourette's syndrome patients (Cohen *et al*, 1980), both illnesses in which increased central dopamine activity may be a factor. Furthermore, apomorphine, a dopamine agonist, increases blink rates in monkeys (Casey *et al*, 1980). The increase is dose-related and the dose response curve shifts to the left after three weeks of haloperidol treatment (Karson *et al*, 1981a). Neuroleptics are dopamine blocking agents and decrease blink rates in schizophrenic patients (Karson *et al*, 1981b) and monkeys (Karson *et al*, 1981c). Taken together, this evidence points to a relationship between central dopamine activity and blink rates (Stevens, 1978).

The clinical potency of neuroleptic medications correlates directly with their ability to block dopamine receptors (Creese *et al*, 1976), presumptive evidence that the antipsychotic actions of neuroleptics are mediated through reduction of dopamine activity. Moreover, it is principally the positive symptoms of schizophrenia (delusions, hallucinations and incoherence of speech) that respond to dopamine blockade by neuroleptics (Johnstone *et al*, 1978b). If blink rates are related to central dopamine activity, the decrease in positive symptoms caused by haloperidol, a dopamine blocking agent, should correlate with a decrease in blink rates. Since the dopamine hypothesis appears to be more relevant in patients with normal cerebral ventricles, the relationship between the change in blink rates and change in symptoms should be stronger in these patients than those with large ventricles.

Patients

The subjects were 17 chronic schizophrenic patients who met Research Diagnostic Criteria (Spitzer *et al*, 1977) for chronic schizophrenia, residing on research wards of the NIMH at Saint Elizabeths Hospital. There were 14 males and three females with a mean age $\pm$ SD of 30.5 ± 6.4 years. Eleven had normal ventricles and six showed ventricular enlargement using the criteria of Weinberger *et al* (1979).

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Methods

As part of a general research programme all patients admitted to the research wards are withdrawn from all neuroleptic medications, and kept drug-free for a minimum of six weeks unless emergent symptoms are severe enough to require shortening of the drug-free period. Patients then are placed on haloperidol 0.4 mg/kg/day for six weeks. Blink rates and behavioural measure tabulations were taken from results obtained during the 5th and 6th weeks of medication withdrawal, and the 5th and 6th week of fixed dose haloperidol treatment. There were two patients who could not complete the protocol as planned. One, a 19-year-old black male became violent while medication-free and was started on fixed dose haloperidol after three weeks. Continuing violence necessitated an increase in medication after another three weeks. The other was a 32-year-old white male who was switched from haloperidol to thioridazine after three weeks because of severe akathesia. In the case of each of these patients, scores were tabulated from the final two weeks of each abbreviated period.

Blinks were observed on Wednesday afternoons during clinical interviews for three consecutive one minute periods by two unobtrusive observers. Blinks counted were averaged and the blink rate expressed as blinks/minute. The average blink rate from observations during the 5th and 6th weeks of fixed dose haloperidol treatment was subtracted from the blink rate determined during the 5th and 6th weeks of the medication withdrawal period, to determine the change in blink rate for each subject. Psychiatric signs and symptoms were measured twice daily by nursing staff using a modified scaled version of the Brief Psychiatric Rating Scale (BPRS) with possible scores from each item varying from 0 (not present) to 6 (most severe). The BPRS items were grouped into five syndromes: anxiety, depression, paranoia, thought disturbance and withdrawal. The thought disturbance syndrome contained disorganized speech, delusions, hallucinatory statements and behaviour. The change in BPRS scores (total and syndromes) was determined by the same method used for blink rates. The change in blink rate was then correlated to the change in BPRS scores by Spearman's correlation coefficient (Siegel, 1956). Blink and behavioural raters were blind to CT scan results of the patients.

Results

For the entire sample, the changes in blink rate correlated only to the change in thought disturbance score ($r = .48$, $P < .05$) (Table I). In normal ventricle patients the changes in blink rate correlated with the changes in total BPRS score ($r = .59$, $P < .05$), the change in thought disturbance ($r = .74$, $P < .01$) and anxiety ($r = .78$, $P < .01$). In the large ventricle group the only significant correlation was a negative one with the change in depression. There were no significant correlations between drug-free blink rates and drug-free BPRS scores, even when the patients were subdivided by ventricular size (in normal ventricle patients r = .07, .28 and −.11 for blink rate versus total, thought disturbance and anxiety scores, respectively).

TABLE I

Correlations of change in blink rate with change in BPRS rating

	Patient group		
	All (N = 17)	Normal ventricle (N = 11)	Large ventricle (N = 6)
Total BPRS score	.32	.59*	−.49
Syndromes from BPRS			
Thought disturbance	.48*	.74**	.20
Withdrawal	.12	.26	−.31
Paranoia	.12	.42	−.31
Anxiety	.37	.78**	−.43
Depression	.11	.15	−1.00*
Activation	.39	.45	.20

* = P < .05.
** = P < .01.

TABLE II

Correlations of change in blink rate with change in BPRS ratings: grouped by ventricular size

	Patient group		
	All males (N = 14)	Males with normal ventricles (N = 9)	Males with large ventricles (N = 5)
Total BPRS score	.62*	.75*	−.10
Syndromes from BPRS			
Thought disturbance	.68**	.75*	.70
Withdrawal	.45	.55	.20
Paranoia	.60*	.80**	.20
Anxiety	.59*	.83**	.00
Depression	.15	.43	−1.00*
Activation	.67**	.63*	.70

* = P < .05.
** = P < .01.

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TABLE III

BPRS scores of relevant syndromes in males grouped by ventricular size and drug status

	Thought disturbance		Paranoia		Anxiety		Activation		Total		Blinks/minute	
Case #	Off*	On**	Off	On	Off	On	Off	On	Off	On	Off	On
Normal ventricles												
1	1.84	1.09	2.85	1.05	1.96	1.15	1.34	.76	2.14	1.41	47.5	25
2	2.05	1.37	2.32	2.13	7.08	1.36	2.33	.98	2.09	1.79	22.6	13.3
3	.93	.85	.62	.57	.52	.63	.16	.19	.95	1.02	29.3	34.2
4	.73	1.81	1.09	1.81	.75	1.06	.08	.43	1.18	1.81	27	45.9
5	1.35	.12	1.15	.14	1.45	.25	.68	.07	1.57	.41	46.3	16.1
6	2.56	.75	1.72	.70	1.48	.57	1.43	.23	2.14	.75	24.3	23
7	.51	.53	.09	.34	.56	.75	.11	.19	.58	.80	9.7	25.2
8	2.83	2.33	.71	.60	1.14	1.18	2.45	1.89	2.06	1.78	20	16.2
9	3.56	1.31	3.36	.19	2.94	.68	1.80	1.28	3.16	1.30	64	51.4
x	1.82	1.12	1.54	.84	1.43	.85	1.15	.66	1.76	1.23	32.3	27.8
±SD	1.03	.67	1.10	.70	.80	.36	.93	.62	.78	.51	16.9	13.4
Large ventricles												
10	3.17	2.98	3.00	2.69	2.50	2.32	2.16	2.37	2.73	2.47	10.3	21.2
11	1.18	.64	1.11	1.20	1.35	1.54	.73	.37	1.41	1.23	42.5	16.5
12	1.80	.65	1.63	1.20	1.27	.73	.71	.28	1.80	1.11	7.3	4.2
13	1.24	.94	1.27	1.65	1.40	.91	.43	.30	1.24	1.09	37	45
14	2.51	1.10	.62	.12	1.25	.70	2.13	.42	1.81	.86	12.9	6.3
x	1.98	1.26	1.53	1.53	1.55	1.24	1.23	.75	1.80	1.35	22.0	18.6
±SD	.85	.98	.90	.95	.53	.69	.84	.91	.58	.64	16.5	16.3

* Off = Drug-free.
** On = Fixed dose haloperidol.

Two of the three females demonstrated a marked difference in the relationship between change in blink rate and the change in psychopathology. Therefore, the patient group was divided by gender for further analysis. Strong correlations between the score changes exist for males (Table II). Table III contains the BPRS scores for each male subject for the syndromes where significant correlations were found in subjects with normal ventricular size. There are no significant differences between the scores for normal and large ventricle patients for any syndrome or blinking while the subjects were drug-free ($u = 21$, 21.5, 21, 20, 22, 14, for thought disturbance, paranoia, anxiety, activation, total, and blinking respectively, $P > .1$ for all items. Mann-Whitney U (Siegel, 1956)).

Discussion

While caution is warranted in interpreting data from only 17 patients, the finding that blink rate changes correlated with changes in psychopathology in chronic schizophrenic patients treated with haloperidol supports the notion that this neurophysiological parameter has some clinical relevance. Moreover, the changes in blink rates correlate most consistently with the changes in the thought disturbance syndrome which measures positive symptomatology. Insofar as positive symptoms are related to increased dopaminergic activity (Johnstone *et al*, 1978b) it would appear that both the antipsychotic activity of haloperidol and decreases in blink rates may be dopaminergically mediated. This finding does not appear to be based on a relative lack of positive symptoms in the large ventricle patients (and the impossibility of neuroleptic response) as demonstrated by the BPRS scores of the male patients while drug-free. Therefore, the presence of these relationships in patients with normal ventricles, and their absence in patients with large ventricles suggests that ventricular size may be relevant in subtyping the schizophrenic syndrome. Moreover, dopamine appears more relevant in patients with normal ventricles as opposed to those with large ventricles.

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