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## Neurological soft signs in schizophrenia and mood disorders

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# CHAPTER 5

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## **THE SPECIFICITY OF NEUROLOGICAL SIGNS IN SCHIZOPHRENIA: A REVIEW.**

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## SUMMARY

This review examines to what extent neurological signs are more prevalent in schizophrenia patients, compared to mood disorder patients and healthy subjects, and whether there is a pattern in any differences that may be found. We included seventeen studies and calculated the weighted mean prevalence of thirty neurological signs. The prevalence of most signs appears to be significantly different between schizophrenia patients and normal controls, but there are fewer differences between schizophrenia and mood disorder patients. Several signs – poor stereognosis and rhythm tapping - are even more prevalent in mood disorder patients than in schizophrenia patients. Only lack of extinction, dysdiadochokinesia, poor tandem walk, finger-thumb-opposition and articulation are significantly more prevalent in schizophrenia compared to mood disorder patients. Impaired motor coordination seems most specific to schizophrenia. The discriminating power of motor sequencing still needs to be studied. So far there is no evidence of a clearly interpretable pattern of neurological signs distinguishing schizophrenia patients from mood disorder patients.

## INTRODUCTION

Minor neurological signs in psychiatric disorders are the focus of an increasing number of studies. Cumulative evidence suggests a higher incidence of neurological signs in schizophrenia compared to normal subjects or to other psychiatric disorders (Heinrichs and Buchanan 1988). However, in other psychiatric disorders neurological signs are also present (Stein et al. 1994;Towey et al. 1993;Heinrichs and Buchanan 1988). Neurological signs have been related to subtypes of schizophrenia; familial- versus sporadic schizophrenia (Kinney et al. 1991;Griffiths et al. 1998), chronic versus acute schizophrenia (Torrey 1980), disorganized versus non-disorganized schizophrenia (Schroder et al. 1992), but could not be related to paranoid versus non-paranoid schizophrenia (Nasrallah et al. 1982;Gureje 1988). Several authors found evidence of lateralisation (Torrey 1980), whereas others did not (Walker and Green 1982). Relations have been found with cognitive functioning (Flashman et al. 1996;Tucker et al. 1975;Kolakowska et al. 1985), emotional stability (Quitkin et al. 1976) and negative symptoms (Caligiuri and Lohr, 1994; Wong et al., 1997). Several studies found a relationship between neurological signs and premorbid adjustment (Gupta et al. 1995;Quitkin et al. 1976;Kolakowska et al. 1985). As some assessment procedures of neurological signs include tardive dyskinesia, obviously both set of symptoms are mixed in these studies. It is unclear whether there is an association between neurological signs and tardive dyskinesia (King et al. 1991;Wegner et al. 1985;Mohr et al. 1996). Most studies focusing on the relation between neurological signs and medication have argued against such relation (Caligiuri and Lohr, 1994; Gupta et al., 1995a; Owens et al., 1982). In a recent review Ismael et al. (1998) found no significant relationships between neurological signs and demographic, etiological or most clinical history characteristics, including past and current neuroleptic exposure. There is substantial evidence of increased neurological signs in non-schizophrenic relatives of schizophrenic patients compared to normal controls (Schreiber et al. 1995;Ismail et al. 1998;Cantor Graae et al. 1994). Sex differences in the level of neurological signs in schizophrenia are not found, but neurological signs in male patients appear to be more dependent on age and du-

ration of illness (Malla et al. 1997; Blyler et al. 1997; Lane et al. 1996). There is no consistent evidence on any predictive value of neurological signs (Bartko et al. 1989; Kolakowska et al. 1985; Johnstone et al. 1990).

There is some evidence that neurological signs correlate with minor neuro-anatomical abnormalities (Mohr et al. 1996; Rubin et al. 1994; Schroder et al. 1991) although other studies failed to replicate these findings (Kolakowska et al. 1985; King et al. 1991; Torrey 1980). Neurological signs might be the result of a global neuropathological dysfunction (Friston and Frith 1995) or reflect localised neuropathological dysfunction (Flashman et al. 1996; Griffiths et al. 1998). In the latter case their pattern might increase our knowledge of causal mechanisms and would probably differ between psychiatric disorders. Several studies have focused on patterns of neurological signs related to neuroanatomical functions (Rubin et al. 1994; Chen et al. 1995; Buchanan and Heinrichs 1989); others on intercorrelations or clusters of neurological signs (Woods et al. 1986; Manschreck and Ames 1984). There is evidence that integrative sensory functions (Griffiths et al. 1998; Walker 1981), motor coordination (Walker 1981; Walker and Green 1982) and motor sequencing (Manschreck et al. 1981; Nasrallah et al. 1982; Manschreck and Ames 1984) are most impaired in schizophrenia patients.

This review focuses on neurological signs in schizophrenia, mood disorders and healthy subjects. Recent studies emphasise the similarities of neuropathological deviations in schizophrenia and mood disorders (Kohler et al. 1998; Taylor 1992; Andreasen et al. 1990). Therefore, it seemed of interest to compare prevalence and pattern of neurological signs in both diagnostic groups.

## **METHODS**

We included all relevant studies on neurological signs in schizophrenic and mood disorder patients. Studies focusing on eye movement disorders have been reviewed elsewhere (Levy et al. 1993) and were excluded. We performed a Medline search including the years 1966-1998 with the search terms: psychiatry and neuro\*, depression and neuro\*, schizophrenia and neuro\*, soft-signs, NSS and tardive dyskinesia. All cross-references from these articles were also examined. This review focuses on three diagnostic groups: (1) schizophrenia spectrum psychotic disorders, including schizophrenia, schizophreniform disorder and schizoaffective disorder; (2) mood disorders including depression and bipolar disorder; (3) healthy control subjects.

We analysed the reported prevalence of specified neurological signs, male/female ratio, age, diagnostic classification, medication (yes/no) and the assessment procedures for neurological signs. We also examined the characteristics of the subjects with mood disorders. Only those neurological signs were included that were assessed in at least two studies. For each sign the weighted mean prevalence for each diagnostic group was calculated by adding the prevalence figures multiplied by number of subjects in the study and dividing this by the total number of subjects in the included studies. Chi-square tests were performed between the diagnostic groups and P-values were corrected for multiple comparisons with the Bonferroni-Holm procedure. A significance level of 0.05 was designated as acceptable. Neurological signs

were classified according to the categories of Buchanan and Heinrichs (1989) and Griffiths et al. (1998): sensory integration, motor coordination, motor sequencing and other. We added 'primitive reflexes' as a fifth category, which has been recognised in previous studies (Chen et al. 1995).

## RESULTS

258 Studies were examined; 17 studies presented useful data on the prevalence of specified neurological signs in one or more diagnostic groups. The number of subjects in the schizophrenia group varied between 93 and 861 (Mean 386, SD 199). In the schizophrenia group the weighted mean prevalence of all 30 signs varied between 3.5 and 60 percent (Mean 19.2, SD 13.7). The number of subjects in the mood disorder group varied between 21 and 104 (Mean 62, SD 23). The weighted mean prevalence of the 17 signs in the mood disorder group varied between 0 and 75.8 percent (mean 16.4, SD 21.7), but they encompassed a smaller selection. The number of subjects in the normal group varied between 42 and 398 (Mean 202, SD 91). The weighted mean prevalence of the 30 neurological signs in the control group varied between 0 and 40.6 percent (Mean 8.9, SD 10.5).

Three studies (Gardner et al. 1997;Manschreck et al. 1982;Nasrallah et al. 1983) used DSM III criteria, seven studies used DSM III-R criteria (Griffiths et al. 1998;Lane et al. 1996;Mohr et al. 1996;Chen et al. 1995;Flashman et al. 1996;Hollander et al. 1990;Gurvits et al. 1993), three studies used the Research Diagnostic Criteria (Wegner et al. 1985;Braun et al. 1995;Kolakowska et al. 1985), two studies used Feighner criteria (Gureje 1988;Cox and Ludwig 1979b), one study used both DSM III and RDC (Buchanan and Heinrichs 1989), one older study was not based on any classification system (Quitkin et al. 1976). Insufficient data is present about drug therapy. Four studies reported antipsychotic therapy in all schizophrenia patients (Braun et al. 1995;Lane et al. 1996;Nasrallah et al. 1983;Chen et al. 1995), six studies reported antipsychotic therapy in the majority of schizophrenia patients (Mohr et al. 1996;Kolakowska et al. 1985;Wegner et al. 1985;Cox and Ludwig 1979b;Buchanan and Heinrichs 1989;Mohr et al. 1996;Manschreck et al. 1982); in one study only 26 percent of schizophrenia subjects used antipsychotic drugs (Quitkin et al. 1976). Three studies did not specify drug therapy (Griffiths et al. 1998;Flashman et al. 1996;Gureje 1988). In the mood disorder group the percentage of patients on antipsychotic drugs is reported in three studies: 80, 62 and 12 percent respectively (Cox and Ludwig 1979b;Manschreck et al. 1982;Quitkin et al. 1976). All normal subjects were without medication. One study did not present data about age (Quitkin et al. 1976). In the remaining studies mean age in the schizophrenia group varied between 29 and 41.3 years; in the mood disorder group mean age varied between 32.5 and 42 years; in the normal group mean age varied between 26.2 and 44.4 years. Four studies did not present data on male/female ratio (Quitkin et al. 1976;Wegner et al. 1985;Kolakowska et al. 1985;Cox and Ludwig 1979b). In the remaining studies the male/female ratio in the schizophrenia group varied between 0.25 and 1, in the mood disorder group between 0.43 and 1, in the normal group between 0 and 1. From the 134 included patients in the mood disorder group, 46 were diagnosed bipolar affective disorder (28 had current manic episode), 19 were diagnosed unipolar affective disorder, 68 were unspecified. All but 16 were consecutive psychiatric inpatients under fifty years old; these 16 patients were selected from the inpatients of a psychiatric hospital.

All studies except one (Nasrallah et al. 1983) explicitly refer to assessment procedures. The exclusion of this study results in fewer subjects in the mood disorder group and as a result in loss of significant differences between the mood disorder group and schizophrenia group on the extinction and palmomental- and suckreflex signs. Most studies refer to one particular publication which describes an assessment procedure, whereas some studies refer to two or more publications (Gureje 1988;Kolakowska et al. 1985;Nasrallah et al. 1983;Lane et al. 1996;Gurvits et al. 1993). Altogether the assessments were based on 14 publications with distinct but minor differences in the assessment procedures (Buchanan and Heinrichs 1989;Convit et al. 1988;Chen et al. 1995;Quitkin et al. 1976;Benton et al. 1951;Cox and Ludwig 1979a;Guy 1973;Manschreck et al. 1982;Dalby 1970;Paulson 1971;Villeneuve et al. 1974;Jenkyn et al. 1975;Torrey 1980;Bender et al. 1951). Two publications accounted for 60 % of the assessment procedures (Buchanan and Heinrichs 1989;Quitkin et al. 1976); three other publications accounted for a further 17 percent (Chen et al. 1995;Cox and Ludwig 1979a;Convit et al. 1988). One of these (Chen et al. 1995) is mainly based on Buchanan and Heinrichs (1989) and Quitkin et al. (1976).

**Table 1.** Prevalence of specific neurological signs per diagnostic group.

			Group					
			Schizophrenia		Mood disorders		Normal Control	
	Sign	references	n	prev (%)	n	prev (%)	N	prev (%)
Sensory integration								
	Extinction	4,6-8,13,15-17	457	17.4	28	0.0	298	1.3
	L-R disorientation	2-4,6,8-17	861	27.9	88	23.2	340	23.5
	Stereognosis	1,3-8,10,13-17	752	16.9	61	36.0	338	11.2
	Graphesthesia	4-6,8-17	777	27.8	100	18.1	340	21.5
Motor coordination								
	Dysdiadochokinesia	6,7,9,11-17	532	13.5	60	1.7	311	3.2
	Tandem walk	6,9,11,15-17	484	10.0	60	0.0	254	2.0
	Finger-thumb opposition	6,8,9,12,13,15-17	451	20.6	60	0.0	244	12.7
	Finger-nose	6,8,10,14-17	541	17.3	0	-	274	10.6
	Rhythm tapping	1,7,10-13,15-17	579	41.8	21	75.8	264	40.6
Motor sequencing								
	Fist edge palm	6,8,13,15,17	267	46.0	0	-	212	15.6
	Oseretski	6,15-17	334	37.2	0	-	254	16.7
	Fist ring	6,8,16,17	303	27.7	0	-	154	9.0
Primitive reflexes								
	Gaze	7,15-17	306	21.7	0	-	207	3.4
	Palmomenta	1,4,6-8,10,13,15,	458	10.5	39	15.4	196	0.5
	Snout	6,7,10,15,17	460	5.3	0	-	197	1.0
	Grasp	1,4,7,8,10,13,15,17	480	8.0	49	14.3	214	2.8
	Suck	6,7,10,17	398	4.5	0	-	97	6.2
Other								
	Trunk/limb dyskinesia	3,15	118	27.5	0	-	100	0.0
	Tremor	6,15,17	236	19.9	0	-	197	4.5
	Convergence	7,16,17	244	26.4	0	-	107	7.6
	Articulation	1,3,9,11,12,14-16	289	16.2	81	0.0	162	3.7
	Saccade	6,15	138	12.9	0	-	147	2.7
	Imaginary acts	1,4,7	113	60.0	49	50.2	49	30.6
	Romberg	6,8,15-17	365	3.5	0	-	254	0.0
	Shuffling gait	8,15	93	7.5	0	-	100	0.0
	Increased gait	9,12,15	148	5.4	60	1.7	115	0.0
	Hopping	8,9,11,12,14,	181	3.9	60	0.0	42	0.0
	Mirror movement	2,4,6,9,12,14-17	534	24.1	104	34.6	365	27.1
	Face hand test	2,8,9,10-12,14	427	10.7	76	8.4	82	4.9
	Extensor Plantar Response	6,8,9,15,	255	4.2	60	0.0	147	3.4

**Table 2.** Bonferroni-Holm corrected *P*-values of chi-square tests between three diagnostic groups.

Sensory integration		S/M	M/C	S/C
	Extinction	0.03	NS	0.001
	L-R disorientation	NS	NS	NS
	Stereognosis	0.001	0.001	0.02
	Graphesthesia	NS	NS	NS
Motor coordination				
	Dysdiadochokinesia	0.02	NS	0.001
	Tandem walk	0.02	NS	0.001
	Finger-thumb opposition.	0.001	0.01	0.01
	Finger nose	-	-	0.01
	Rhythm tapping	0.001	0.001	NS
Motor sequencing				
	Fist edge palm	-	-	0.001
	Oseretski	-	-	0.001
	Fist ring	-	-	0.001
Primitive reflex				
	Gaze	-	-	0.001
	Palmomental	NS	0.001	0.001
	Snout	-	-	0.01
	Grasp	NS	0.001	0.02
	Suck reflex	-	-	NS
Other				
	Trunk/limb dyskinesia	-	-	0.001
	Tremor	-	-	0.001
	Convergence	-	-	0.001
	Articulation	0.001	NS	0.001
	Saccade	-	-	0.001
	Imaginary acts	NS	NS	0.001
	Romberg	-	-	0.001
	Shuffling gait	-	-	0.01
	Increased gait	NS	NS	0.03
	Hopping	NS	-	NS
	Mirror movement	NS	NS	NS
	face hand test	NS	NS	NS
	Extensor Plantar response	NS	NS	NS

NS= Non significant ( $p>0.05$ )

S/M= Schizophrenia versus Mood disorders

M/C= Mood disorders versus Normal Controls

S/C= Schizophrenia versus Normal Controls

**References Table 1:**

- 1= (Cox and Ludwig 1979b)
- 2= (Gureje 1988)
- 3= (Kolakowska et al. 1985)
- 4= (Nasrallah et al. 1983)
- 5= (Manschreck et al. 1982)
- 6= (Griffiths et al. 1998)
- 7= (Lane et al. 1996)
- 8= (Braun et al. 1995)
- 9= (Quitkin et al. 1976)
- 10= (Flashman et al. 1996)
- 11= (Wegner et al. 1985)
- 12= (Walker 1981)
- 13= (Gurvits et al. 1993)
- 14= (Hollander et al. 1990)
- 15= (Chen et al. 1995)
- 16= (Mohr et al. 1996)
- 17= (Buchanan and Heinrichs 1989)

Table 1 shows the weighted mean prevalence of specified neurological signs for each diagnostic group. The first column gives the neurological signs. The second column shows the numbers corresponding to the studies included. For each diagnostic group the column "n" gives the total number of subjects for each sign. The column "prevalence" gives the weighted mean percentage of patients who showed a particular neurological sign in the studies included.

Table 2 shows the Bonferroni-Holm corrected P-values of Chi-square tests between the diagnostic groups. The first column gives the neurological sign. The columns S/M, M/C and S/C give the corrected P-values of the Chi-square tests between schizophrenia (S), mood disorder (M) and normal control (C) groups.

## DISCUSSION

Several limitations in interpreting the data must be pointed out. The available data did not allow control of demographic and clinical variables. This unfortunately also rules out the possibility of examining gender effects. Furthermore, the number of subjects in the mood disorder group is small. As a result, differences in neurological signs between the mood disorder group and other groups may not have reached significance due to limited statistical power. Also, because the small number of studies in this group, some studies could be outweighed. Although there is consistency in the assessment procedures, the possibility of assessment bias can not be ruled out.

The results are noteworthy in several respects. First, the weighted mean prevalence of most signs is significantly different between schizophrenia patients and normal controls, but there are fewer differences between schizophrenia and mood disorder patients. Second, several signs -poor stereognosis and rhythm tapping - are more prevalent in mood disorder patients than in schizophrenia patients. Third, only poor extinction, dysdiadochokinesia, tandem walk, finger-thumb-opposition and articulation are significantly more prevalent in schizophrenia compared to mood disorder patients. Fourth, a number of signs, notably motor sequencing signs, have not been studied in mood disorder patients, so that their specificity can not be estimated.

There is no evidence of categories of neurological signs that unequivocally distinguish schizophrenia patients either from healthy controls or from mood disorder patients, nor of another clearly interpretable pattern of neurological signs. Motor sequencing deserves more attention, but before more data are available, speculations would be premature. Signs of compromised motor coordination seem to be most specific for schizophrenia patients although poor rhythm tapping is more prevalent in mood disorder. However, the prevalence figures of this sign in the mood disorder group are based on a very limited sample. The overall impression is that the specificity of neurological signs for the diagnosis of schizophrenia tends to be overrated.

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