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Neurological signs and sustained attention impairment in schizophrenia

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Abstract Both neurological signs and attention impairments are often found in schizophrenia. This study addresses the extent to which neurological signs are related to sustained attention impairment. We assessed subgroups of neurological signs using the standardised Cambridge Neurological Inventory (CNI). Sustained attention was measured using a monotone counting paradigm. After taking into consideration potential confounds such as age, education level and duration of illness, we explored the correlation between sustained attention and groups of neurological signs, as well as with individual signs. We found that "motor coordination" and "disinhibition" signs were significantly related to sustained attention. The correlation with "sensory integration" just failed to reach significance after correction for multiple comparison. "Dyskinesia", "catatonia", "pyramidal" and "extrapyramidal" subgroups were unrelated to sustained attention. The results support the notion of heterogeneity and diversity in neurological signs (even among soft neurological signs) and argue against the use of a single global measure to embrace all soft neurological signs in schizophrenia.

Key words Attention · Neurologic manifestations · Cognition · Schizophrenia

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Introduction

Increased prevalence of neurological signs has been consistently reported in schizophrenic patients. These include neurological soft signs (NSS) (Kinney et al. 1993, Quitkin et al. 1976, Rochford et al. 1970, Tucker et al. 1975, Walker et al. 1982), "pyramidal" signs (Kinney et al. 1993, Woods et al. 1991), "extrapyramidal" signs (Simpson et al. 1970, Simpson et al. 1979), "dyskinesia" (Owens et al. 1982) and "catatonia" (Lund et al. 1991, Manschreck et al. 1982). In schizophrenia, neurological signs are detected in the absence of coarse brain disease and they have generally been considered as markers for a putative brain vulnerability factor (King et al. 1991, Kolakowska et al. 1985, Marcus et al. 1985a, Woods et al. 1987). NSS are also found to be more prevalent amongst medication-naive schizophrenic patients (Gupta et al. 1995), as well as amongst children genetically at risk for schizophrenia (Erlenmeyer-Kimling et al. 1989, Marcus et al. 1985b, McNeil et al. 1993, Rieder et al. 1979).

Despite the lack of localisation significance for NSS in the conventional neurological sense, there are some recent supports for a degree of specificity in their mapping onto defined cortical areas (Merriam et al. 1990, Schroder et al. 1992). Correlation between motor soft signs and the size of the basal ganglia has been reported (Schroder et al. 1992). In addition, a functional Magnetic Resonance Imaging (MRI) study of repetitive motor movement (similar to "motor coordination" signs) has identified specific activation of the supplementary motor area and the sensorimotor cortex (Schroder et al. 1995).

Another important issue concerning neurological signs in schizophrenia is the extent to which they relate to basic cognitive processes such as attention. Like neurological signs, impairments in sustained attention have been consistently found in schizophrenic patients (Cornblatt et al. 1985, Cornblatt et al. 1988, Cornblatt et al. 1989, Everett et al. 1989) and in children at high risk for schizophrenia (Erlenmeyer-Kimling et al. 1992,

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Rutschmann et al. 1986). Similar findings have also been reported among the first-episode medication-naive patients (Saykin et al. 1994) which indicates that attention deficit is unlikely to be related to medication treatment (Nestor et al. 1991, Serper et al. 1994, Strauss et al. 1985).

Although sustained attention is now considered to be a process required for the execution of a variety of cognitive and motor functions (LaBerge 1995), the extent to which attentional impairment underlies the manifestation of neurological signs is a relatively unexplored empirical question. In one related study, total NSS scores were found to be specifically correlated only with those cognitive tests involving timed motor responses (Flashman et al. 1996). However, there have been few investigations into the relationship between attention and various subgroups of neurological signs.

In this study, we aimed to investigate the relationship between sustained attention and subgroups of neurological signs in schizophrenia. We intended to identify individual signs or subgroups of signs in which attention plays an important role. We assessed sustained attention with a simple auditory task (adapted from Wilkins et al. 1987) in which detection of attention deficit does not depend upon its coincidence with stimulus being presented. Being considerably shorter than the continuous performance test, the monotone counting task also appeared to be better tolerated by patients. Previous neuropsychological validation study has indicated that sustained attention deficit (tapped by this task) is particularly related to right prefrontal cortex instead of left frontal or temporal cortices (Wilkins et al. 1987). This neuropsychological localisation pattern is similar to those addressed by the continuous performance test (Cohen et al. 1992, Guich et al. 1989).

Method

Subjects

After ethics committee approval, patients between the age of 16 and 65 years meeting DSM-III-R diagnostic criteria for schizophrenia (American Psychiatric Association 1987) were recruited from acute and continuing care inpatient facilities in Hong Kong. Diagnosis according to DSM-III-R was ascertained by the research psychiatrists (EYHC, LCWL, RYLC, DGHN) with a clinical interview as well as information from case records and informants. Consenting subjects were carefully screened and those with substance abuse, organic disorder, mental retardation, as well as a history of electroconvulsive therapy (during the previous 2 years) were excluded from the present study.

Assessment of clinical picture

Symptom assessments were carried out with the 18-item Brief Psychiatric Rating Scale (BPRS) (Overall et al. 1962). The BPRS has been successfully applied in the Hong Kong Chinese population (Chan et al. 1993). The intraclass correlation coefficient for BPRS items ranged from 0.84 to 0.99 (Bartko et al. 1976). Neuroleptic dosages were converted to chlorpromazine equivalent (Davis 1974). Anti-cholinergic dosage was recorded in mg benzhexal per day. Handedness was assessed with a standardised instrument (Annett 1970). Intelligence level was measured with four of the verbal subscales (digit span, information, similarities, and comprehension) from the Weschler Adult Intelligence Scale WAIS-R-HK (Revised Cantonese Version, 1989).

Assessment of sustained attention

To assess sustained attention, a simple auditory paradigm was carried out by asking subjects to silently count regularly-paced monotones (adapted from Wilkins et al. 1987). Trains of brief pure tones (360 Hz frequency, 250 msec duration) generated at a regular pace (one tone per sec) were presented by a loudspeaker to patients. The number of tones in each trial varied from 1 to 12 in a randomised order. Each patient completed 12 trials. An instruction was given at the beginning of each trial. Patients were asked to report the number of tones presented after finishing each trial. The number of correct counts was then recorded (maximum 12, minimum 0).

Assessment of neurological signs

Neurological signs were examined by a separate examiner (blind to the results of the monotone counting task) using the Cambridge Neurological Inventory (CNI) (Chen et al. 1995). The CNI offered standardised procedures for rating the neurological signs in seven subgroups. These groups were made according to the nature of individual item of signs (Chen et al. 1995). The "motor coordination" subgroup consisted of *finger-thumb opposition, finger-thumb tapping, dysdiadochokinesia, fist-edge-palm test* and *Ozeretski test*. The "sensory integration" subgroup included *extinction, finger agnosia, stereoagnosia, graphaesthesia* and *left-right disorientation*. The "extrapyramidal" subgroup included *glabellar sign, increased limb tone, decreased associated movements in walking, shuffling gait, arm-dropping test, tremor* and *neck rigidity*. The "dyskinesia" subgroup included *trunk-limb dyskinesia* and *orofacial dyskinesia*. The "catatonia" subgroup included *gait mannerism, gegenhalten, mitgehen, imposed posture, exaggerated spontaneous movements, abrupt smooth spontaneous movements, iterative spontaneous movements, mutism, automatic obedience, echopraxia* and *perserveration*. The "disinhibition" subgroup included *blinking during saccadic eye movement, lateral head movement during saccadic eye movements, unilateral winking, mirror movements (during finger tapping and dysdiadochokinesia)* and *go-nogo test*. "Pyramidal" subgroup included *plantar reflexes, hyperreflexia, hyporeflexia* and *decreased power in extremities*. Each of these signs was rated either 0 (absent), 1 (present), or 2 (strongly present) as applicable and in accordance with standardised instructions. A subgroup score was calculated by summing the scores for individual signs within the group. Inter-rater reliability was established by rating on a sample of 15 patients not included in this study. The overall intraclass correlation coefficient was 0.94.

Data analysis

Neurological signs scores and sustained attention scores showed a positively skewed distribution, therefore logarithmic transformation was carried out before parametric analysis (e. g. Pearson correlation coefficient and partial correlation coefficient). For sustained attention score and neurological signs scores, the transformation was carried out by adding 1 to the sum of error (number of tones missed) and then taking the natural logarithm of the sum. For analysis of correlation between individual sign score and sustained attention, the non-parametric Spearman rank coefficient was used.

Results

Demographic and clinical data for the sample

Two hundred and four schizophrenic patients were recruited in this study (122 male, 82 female). Mean age of patients was 40.5 years (SD 12.2 years) and the mean duration of illness was 15.1 years (SD 9.8 years). The mean education level was 8.0 years (SD 3.4 years). The mean scaled scores for WAIS-R-HK subtests were as follows: information (6.2 SD 2.7); digit span (9.2, SD 3.2); comprehension (5.2 SD 3.2); and similarities (4.4 SD 3.2). The mean BPRS score was 30.0 (SD 7.2) for the entire sample and 29.9 (SD 7.19) for right-handed subjects. The mean daily anti-psychotic dosage was 940 mg (SD 1007 mg) of chlorpromazine equivalent, whereas the mean daily dosage of benzhexal was 3.2 mg (SD 3.3 mg). There is no significant correlation between BPRS scores, medication dosage and NSS scores. The proportions of patients in which more than one sign is present are as follows: motor coordination (48 %); sensory integration (51 %); disinhibition (47 %); catatonia (10 %); pyramidal (6 %); extrapyramidal (41 %); and dyskinesia (5 %).

Relationship between sustained attention and subgroups of neurological signs

Among the seven subgroups of neurological signs, sustained attention was significantly correlated with "motor coordination" (Pearson correlation coefficient 0.43, $p<0.001$), "sensory integration" (Pearson correlation coefficient 0.33, $p<0.001$) and "disinhibition" (Pearson correlation coefficient 0.34, $p<0.001$). Since previous work has identified correlation between sustained attention and age, education level and duration of illness (Chen et al. 1997), partial correlation coefficient was carried out to control for these confounding effects (Table 1). The results indicated that "motor coordination" and "disinhibition" were still significantly correlated with sustained attention impairment, whereas "sensory integration" just fell short of significance after Bonferroni correction for multiple comparison. In contrast, none of the other groups of signs were found to be correlated with sustained attention.

Relationship between sustained attention and individual neurological signs

The relationship between individual neurological signs and sustained attention was explored with Spearman correlation coefficient. The significance level was adjusted to $p<0.001$ for multiple comparison by the Bonferroni method. Signs which were significantly correlated with sustained attention are shown in Table 2. Signs that were strongly correlated (Spearman coefficient >0.3) included *fist-edge-palm test, go-nogo test, Ozeretski test, rhythm tapping* as well as *articulation*. Signs that were moderately correlated (Spearman coefficient between 0.2 and 0.3) included most remaining signs in the "motor coordination" and "sensory integration" subgroups.

Is there a lateralised relationship with neurological signs?

Data obtained from 167 right-handed subjects was further analysed to explore if there was any lateralised pattern of correlation between sustained attention and neurological signs. Signs which could be lateralised (i. e.

Tab. 1 Partial correlation coefficient between sustained attention and subgroups of neurological signs controlling for age, education level and duration of illness.

"Motor Coordination"	"Sensory Integration"	"Extrapyramidal"	"Dyskinesia"	"Catatonia"	"Disinhibiton"	"Pyramidal"
0.26 P=.000	0.19 P=.010	0.13 P=.088	–0.01 P=.859	0.12 P=.110	0.22 P=.003	0.06 P=.383

* Level of significance after Bonferroni correction for multiple comparison is adjusted to $p<0.007$.

Tab. 2 Spearman coefficient between sustained attention and individual signs among "motor coordination", "sensory integration" and "disinhibition" subgroups.

"Motor Coordination" signs						
FEP (L)	FEP (R)	Ozereski (L)	Ozereski (R)	Finger-thumb opposition (L)	Finger-thumb opposition (R)	Finger thumb Tapping (L)
–0.40 Sig. 000	–0.37 Sig. 000	–0.35 Sig. 000	–0.33 Sig. 000	–0.27 Sig. 000	–0.30 Sig. 000	–0.23 Sig. 001

"Sensory Integration" signs						*"Disinhibition" signs*	
Rhythm Tapping	Finger Agnosia (L)	Finger Agnosia (R)	Astereoagnosia (L)	Agraphaesthesia (L)	Agraphaesthesia (R)	Unilateral winking	Go-no go
–0.33 Sig. 000	–0.24 Sig. 001	–0.26 Sig. 000	–0.25 Sig. 001	–0.25 Sig. 001	–0.25 Sig. 001	–0.23 Sig. 001	–0.36 Sig. 000

* Level of significance after Bonferroni correction for multiple comparison is adjusted to $p<0.003$.

could be elicited either in the left or the right) belong to "motor coordination" *(finger-thumb opposition, finger-tapping, fist-edge-palm)* and "sensory integration" *(finger agnosia, agraphaesthesia, astereoagnosia)* subgroups. Partial correlation coefficient was carried out to control the confounding effect of age, education level and duration of illness. Left "motor coordination" signs were correlated (Partial correlation coefficient 0.31, $p<0.001$) at a similar level as right "motor coordination" signs (Partial correlation coefficient 0.29, $p<0.001$). Likewise, left "sensory integration" signs were correlated (Partial correlation coefficient 0.18, $p=0.018$) at a similar level as right "sensory integration" signs (Partial correlation coefficient 0.17, $p=0.026$). This pattern still held when the entire sample (regardless of handedness) was analysed.

Discussion

The results of this study indicated that sustained attention performance was correlated with particular groups of neurological signs in a highly specific manner. This leads to two important considerations. Firstly, some neurological signs in schizophrenia are not "pure" physical signs in that their manifestations may involve some cognitive processes such as attention. Secondly, the extent of cognitive involvement is different for different groups of signs. This highlights a fundamental heterogeneity amongst neurological signs that are found to be increased in schizophrenia.

It is noteworthy that sustained attention was more related to the "motor coordination" and "disinhibition" subgroups of neurological signs. In contrast, no significant correlation was found between sustained attention and "sensory integration", "dyskinesia", "catatonia", "extrapyramidal" signs as well as "pyramidal" signs. Conventionally, "signs" refer to observable clinical features that could be reliably elicited in a standardised bedside examination. As such, they should be relatively independent of conscious control. However, in situations where neurological signs address brain areas concerned with higher cognitive functions (such as the prefrontal cortex), interplay between neurological signs and cognition may be inevitable. Such interplay may involve two possible mechanisms. Firstly, in order to perform the response required, attentional resources are inherently involved (functional link). Secondly, the neurological signs and attentional process may just happen to map onto overlapping cortical regions and are, therefore, more likely to be affected together in any disease process (topographical link). Although this study was not designed specifically to distinguish these mechanisms, circumstantial evidence suggests that the second mechanism (topographical link) is probably less likely. Firstly, sustained attention and motor coordination signs appear to map onto distinct cortical areas. Functional neuroimaging data suggested that "motor coordination" involves the sensorimotor cortex and supplementary motor area (Schroder et al. 1995), whereas sustained attention involves the right prefrontal cortex (Cohen et al. 1992, Guich et al. 1989, Wilkins et al. 1987). Secondly, if topographical link were important, a lateralised pattern of correlation (stronger correlation between attention and neurological signs on the right side) would be expected since the sustained attention task maps onto the right prefrontal cortex. Our finding of the lack of lateralised pattern of correlation therefore speaks against this mechanism. Thus, we tentatively suggest that a functional link is more likely to have been a possible basis for the observed correlation between sustained attention and NSS. Clearly, this is an area that deserves further investigation.

The differential extent of affiliation to attention also suggests a criterion for empirical classification of neurological signs. Firstly, the NSS ("motor coordination", "sensory integration" and "disinhibition") as a group is contrasted with other groups of signs ("catatonia", "dyskinesia", "pyramidal" and "extrapyramidal" signs) in that they covariate with age, education level and duration of illness, whereas other groups of signs do not. Further grouping among NSS can be demarcated by removing the covariance with age, education level and duration of illness. The results revealed a specific relationship between sustained attention, "motor coordination" and "disinhibition" subgroups, but less so with "sensory integration" subgroup. This pattern of correlation was also confirmed by computing correlation coefficient for individual signs. In this way, the extent of affiliation to attention can be considered as a potential criterion by which subgroups of neurological signs of relevance to schizophrenia could be delineated. This finding also suggests that neurological signs, in particular NSS, found in schizophrenia are heterogeneous and should not be summarised by just one single score. If correlational analysis was entirely based on a single summary score for all NSS, potentially significant information could be masked.

This study demonstrated that there is a clear relationship between sustained attention impairment and specific groups of neurological signs. The results suggest that sustained attention may functionally underlie the manifestation of these signs. These findings contribute to an understanding of the nature of neurological deficits in schizophrenia from a cognitive perspective.

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