Executive Dysfunctions and Neurological Manifestations in Schizophrenia

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Abstract

Objective: To further explore the relationship between a set of executive function factor scores and neurological features in patients with chronic schizophrenia.
Patients and Methods: This cross-sectional study investigated the Sustained Attention Response to Task, Six Elements Test, Hayling Sentence Completion Test, and Cambridge Neurological Inventory in 51 patients with schizophrenia.
Results: Significant relationships were found between executive function factors and neurological signs after adjustment for the confounding effects of age, education, illness duration, and medication.
Conclusion: The derived factors seem to share common neural substrates with neurological soft signs in schizophrenia. Neurological soft signs could be adopted by clinicians as a bedside screening test of executive dysfunctions.

Key words: *Dementia, Neurological manifestations, Schizophrenia*

Introduction

Schizophrenia is a brain disorder affecting subjective experiences as well as a number of cognitive functions. Experimental and clinical studies adopting both cross-sectional[1-3] and longitudinal designs[4-5] also demonstrate that specific domains are differentially affected against a background of diffuse impairment in addition to a global decline in intellectual functioning.[6] Consistent evidence of the major involvement of the frontal lobes in schizophrenia has been shown in a wide range of studies.[7-12] These studies suggest that the frontal lobe, particularly the prefrontal region, is one of the main sites of abnormality in schizophrenia. Damage in this region has been shown to be associated with poor planning and mental rigidity,[13] impaired social judgement,[14] and impulsivity[15] collectively known as dysexecutive syndrome.[16] Impairments in executive functions are most obvious as patients attempt to cope with the complexities, open-ended situations, and social ambiguities of everyday life.

Recent research into executive function performance in clinical groups has emphasised the application of the 'new generation tests', which are primarily derived from theory of executive functions. The supervisory attention system[17,18] is one of the most frequently used models for explaining cognitive disorders in patients with frontal lobe lesions,[17-19] normal healthy adults,[20] and clinical symptoms in schizophrenia.[21] The supervisory attention system plays a major role in regulating the non-routine and novel task performance in daily life. Impairment of this system would be expected to result in a wide range of deficits in goal setting, planning, and making decisions between alternative sequences of behaviour in order to reach a particular goal.

The crucial role of neurological abnormalities or signs in schizophrenia has been recognised by Tsuang and Faraone as the 'target features' that encompass the idea that genetic and non-genetic processes lead to maldevelopment in neurocognitive systems.[22] Target features should be increased in relatives of patients but perhaps not to a similar extent. In addition, the manifestation of multiple genes of small effect would lead to an expectation that target features should be present, to a lesser extent, in the general population. Neurological signs, therefore, also represent a potential intermediate phenotype in schizophrenia.[23] In particular, the relationship between neurological soft signs and neuropsychological performance deficits in schizophrenia have recently been gaining more attention. The term 'soft signs' is used in contrast to 'hard signs', which are localisable to specific brain regions and typically involve motor or

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perceptual systems. The boundary between neuropsychology and neurological signs is not sharp and uncontentious. It was not until recently that a few studies began to explore the relationships between specific domains of neurological signs and executive functions.[24-26] In general, the frontal signs or soft neurological signs (motor coordination, sensory integration, and disinhibition) were significantly correlated with various neuropsychological dysfunctions. Wong et al found that the frontal signs were associated with random errors of the executive functions.[26] Ross et al also found that the sensory integration item was the most frequent predictor of eye-tracking performance in patients with chronic schizophrenia.[25] These studies demonstrated that the frontal signs were the most discriminatory items in classifying these patients. Chen et al demonstrated that a frontally based attention task was strongly correlated with motor coordination and disinhibition but not the other signs in a group of patients with chronic schizophrenia.[27]

Most recently, Chan et al successfully demonstrated the construct validity of a set of executive function tests based on the supervisory attention system in patients with schizophrenia.[28] Three factors were identified within the executive function tests, as follows:

- the 'semantic inhibition factor' comprised items inhibiting verbal and semantic responses
- the 'action/attention inhibition' factor comprised items on error commission and rule-breaking score
- the 'output generation factor' comprised items on initiation and generation of response.

This brief report further discusses the relationship between these derived factors and neurological signs in a group of patients with schizophrenia and suggests that frontally based tasks might functionally underlie the manifestation of specific neurological soft signs in schizophrenia.

Patients and Methods

Fifty one inpatients with chronic schizophrenia (47 men and 4 women) were recruited at a regional psychiatric hospital. All patients met the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for schizophrenia. Informed consent was obtained from all patients prior to the testing session in accordance with the Declaration of Helsinki. The mean age was 44 years (standard deviation [SD], 9.58 years) and the educational level was 8.2 years (SD, 2.86 years). The mean illness duration was 21.3 years (SD, 9.5 years). The mean daily antipsychotic drug dose was 1263.13 mg chlorpromazine equivalents (SD, 1577.74 mg; range, 700.00 to 7143.00 mg). All participants were right-handed according to the Edinburgh Inventory.[29] The Positive and Negative Syndrome Scale (PANSS) was used for the assessment of symptoms.[30] All items were rated from 1 (absent) to 7 (extreme) according to the standardised instructions. Inter-rater reliability for the PANSS was evaluated with the intra-class correlation coefficient (ICC). ICC was 0.83 for the global PANSS score, 0.84 for the positive symptoms subscale, and 0.73 for the negative symptoms subscale.

The details of the executive function tests selected for the study are described elsewhere.[28] The tests used were the Sustained Attention Response to Task (SART),[31] the Six Elements Test (SET),[32] and the Hayling Sentence Completion Test (HSC).[19] The applicability of these measures has also been validated in the Hong Kong setting.[20,28,33,34] Background cognition tests, including the short-form of the Wechsler Adult Intelligence Test-III[35] and the Logical Memory and Visual Reproduction Tests of the Wechsler Memory Test-III[36] were administered to all participants before the neuropsychological session. Table 1 summarises the qualitative features of these tests.

Neurological signs were examined using the Cambridge Neurological Inventory (CNI).[37] The CNI offered standardised procedures for rating neurological signs in 7 subgroups according to the nature of individual items of these signs. These are 'motor coordination' (e.g., finger/thumb opposition), 'sensory integration' (e.g., finger agnosia and stereoagnosis), 'extrapyramidal' (e.g., glabellar signs and neck rigidity), 'dyskinesia' (e.g., trunk limb dyskinesia and orofacial dyskinesia), 'catatonia' (e.g., gait mannerisms and perseveration), 'disinhibition' (e.g., blinking during saccadic eye movements and go-nogo test), and 'pyramidal' (e.g., hyper- and hyporeflexia). In the original ratings scale, scoring was done according to standardised anchor points

Table 1. Description of the tests used in the study.

Test	Qualitative features
Background cognition	
Wechsler Adult Intelligence Test-III	Verbal performance: information, arithmetic, digit forward and backward span
Wechsler Memory Test-III	Verbal memory: logical memory immediate score Visual memory: visual reproduction immediate score
Executive function tests	
Sustained Attention Response to Task	Deficiency score: number of correct responses Excess score: number of commission errors
Six Elements Test	Deficiency score: raw score of the task according to the standard manual Excess score: total number of rule-breaking responses
Hayling Sentence Completion Test (Part B)	Deficiency score: number of correct responses Excess score: number of errors in categories A and B

to indicate a 'normal' response (0), an 'equivocal' response (0.5), an 'abnormal' response (1.0), or a 'grossly abnormal' response (2.0). In the present study, item scores were further abbreviated into either absent (0; covering normal or equivocal scale scores) or present (1; covering abnormal or grossly abnormal scale scores). Inter-rater reliability was established by rating a sample of 15 of the patients in this study. The overall intra-class correlation coefficient was 0.94.

The composite scores of the derived factors[28] were first computed by adding the standardised scores of the corresponding factor and were used for subsequent data analysis. Pearson product-moment correlations, controlling for age, education, duration of illness, and medication, were conducted to investigate the relationship between the factor composite scores and subscales of the neurological signs. For the analysis of the potential involvement of the executive function in the manifestation of soft neurological signs, a series of multiple linear regression analyses were conducted. Individual neurological sign scores were treated as the dependent variables and neuropsychological domain scores were treated as the independent variables.

Results

There were significant correlations between age and motor coordination (r = 0.318; p = 0.023), sensory integration (r = 0.347; p = 0.013), logical memory immediate recall (r = -0.289; p = 0.04), visual reproduction immediate recall (r = -0.383; p = 0.006), and visual reproduction delayed recall (r = -0.316; p = 0.024). However, for educational levels, a significant correlation was found only in verbal performance (r = 0.398; p = 0.012). The duration of illness was also correlated with sensory integration (r = 0.336; p = 0.017), extrapyramidal signs (r = 0.308; p = 0.029), and catatonia (r = 0.303; p = 0.032).

Partial correlation analyses, controlling for age, education, illness duration, and medication, revealed a series of significant correlations between the executive function factor scores, different subscales of neurological signs, and background cognition. Table 2 indicates that, among the 7 subgroups of neurological signs, the action/attention inhibition factor was significantly correlated with motor coordination (r = 0.346; p = 0.023). There was also a trend for correlation between this factor and sensory integration (r = 0.262; p = 0.09) and disinhibition (r = 0.273; p = 0.077). Significant inverse correlations were found between the output generation factor and sensory integration (r = -0.4; p = 0.008).

Significant inverse correlations were also found between visual reproduction and motor coordination (r = -0.388; p = 0.021), sensory integration (r = -0.503; p = 0.002), disinhibition (r = -0.331; p = 0.05), and extrapyramidal signs (r = -0.358; p = 0.035). Logical memory was also correlated with sensory integration (r = -0.448; p = 0.007). Finally, verbal performance was inversely correlated with motor coordination (r = -0.322; p = 0.05), sensory integration (r = -0.586; p = 0.0005), and disinhibition (r = -0.349; p = 0.04).

The relationships between executive function factors and individual neurological soft signs (motor coordination, sensory integration, and disinhibition) were further explored. For motor coordination, the action inhibition factor was correlated with finger-thumb tapping for the left side (r = 0.26; p = 0.05), fist/edge/palm for the right side (r = 0.317; p = 0.038), and the Ozeretski test (r = 0.368; p = 0.015). For sensory integration, the semantic inhibition factor was inversely correlated with finger agnosia for the right side (r = -0.31; p = 0.04). The action/attention inhibition factor was correlated with extinction (r = 0.442; p = 0.003) and left/right orientation (r = 0.355; p = 0.019) and inversely correlated with graphaesthesia for the left side (r = -0.271; p = 0.05). The output generation factor was inversely correlated with finger agnosia for the right side (r = -0.329; p = 0.031), left graphaesthesia (r = -0.269; p = 0.05), and left/right orientation (r = -0.315; p = 0.04). For disinhibition, the action inhibition factor was significantly correlated with the go-nogo item (r = 0.377; p = 0.013).

For neurological signs as dependent variables, significant neurocognitive contributors to motor coordination signs included the action/attention inhibition score and the memory

Table 2. Partial correlation coefficients between executive function factor scores, background cognition, and subgroups of neurological signs.

Neurological signs	Verbal performance	Logical memory (immediate)	Logical memory (delayed)	Visual reproduction (immediate)	Visual reproduction (delayed)	Semantic inhibition	Action/ attention inhibition	Output generation
Motor coordination	-0.322*	-0.262	-0.048	-0.388*	-0.235	0.088	0.346*	-0.07
Sensory integration	-0.586*	-0.448*	-0.392*	-0.503*	-0.51*	-0.107	0.262†	-0.4*
Extrapyramidal signs	-0.108	-0.102	-0.098	-0.358*	-0.222	-0.015	0.249	-0.204
Dyskinesia	-0.03	-0.017	0.042	-0.131	-0.14	-0.032	-0.015	0.054
Catatonia	0.06	-0.129	-0.074	-0.314†	-0.226	0.107	0.109	-0.188
Disinhibition	-0.349*	-0.031	-0.242	-0.331*	-0.134	0.061	0.273†	0.026
Pyramidal signs	0.211	-0.086	0.103	0.066	0.088	0.084	-0.106	0.006

** $p < 0.05$.*

† Correlation coefficient >0.3 and $p < 0.1$.

composite score [F(2,32) = 5.706; p = 0.008]. Significant contributors to sensory integration signs included only the memory composite score [F(1,33) = 14.364; p = 0.0006]. The neurocognitive function and executive functions were not found to be predictive of disinhibition signs and other hard neurological signs.

Discussion

These findings indicate that significant but modest relationships were differentially demonstrated among these variables, taking into account age, education, and the duration of illness, as well as medication. Among these neurological signs, motor coordination, sensory integration, and disinhibition signs have traditionally been regarded as soft neurological signs, largely on conceptual and theoretical bases.[38] In contrast with other groups of hard neurological signs, we have found that soft neurological signs are more cohesively related to one another and are particularly closely related to impairments in the executive functions. However, no significant correlation was found among the executive function factors and other hard neurological signs such as extrapyramidal and catatonic signs. These findings are consistent with previous studies[26,39] — namely, that the neurological signs could be subclassified into frontal signs and soft neurological signs. Importantly, the relationship with cognitive deficits appears to be specific and different for 2 subgroups of soft neurological signs (motor coordination and sensory integration). These results therefore provide some empirical support for the classification of soft neurological signs into motor coordination and sensory integration subgroups.[40]

Motor coordination signs were specifically associated with impairments in action and attention inhibition, as well as with verbal performance and visual memory. It is noteworthy that verbal performance has also been related to general intelligence and executive function, and it has been suggested that frontal lobe function is critically involved.[41] In this context, it is not surprising that motor coordination signs were significantly related to both verbal performance and executive function components. Sensory integration signs were generally related to a wider range of neurocognitive functions in addition to executive functions. In schizophrenia, there is evidence for a generalised cognitive decline, which affects performance in verbal functioning.[42] The extremely strong association between sensory integration and verbal performance suggests that the presence of the latter is probably a reflection of a generalised cognitive impairment. The present data also suggest that disinhibition signs are also specifically related to the action/attention inhibition component of the executive functions. Item by item analysis revealed a specific relationship between the go-nogo test and the action/attention inhibition factor of executive function.

This brief report is limited by a number of methodological issues. In light of the total number of correlations, the significant correlations found between the executive function factors and neurological signs might warrant multiple group comparison adjustment. However, in view of the exploratory nature of this report, it is still worthwhile and relevant to the understanding of the underlying neural substrates between neurological signs and executive functions to a certain extent. Future study should recruit a larger sample with stringent statistical analysis controlling for multiple comparison adjustment. This study is one of very few studies to explore the relationship between executive functions and neurological signs in schizophrenia using supervisory-attentional-based measures.

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