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EXPANDING THE SCHIZOPHRENIA PHENOTYPE: A COMPOSITE EVALUATION OF NEURODEVELOPMENTAL MARKERS

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Abstract

Minor Physical Anomalies (MPA) and Neurological Soft Signs (NSS) have been consistently reported to be more frequent in schizophrenia subjects and their first-degree relatives. We aimed at co-assessing both these neurodevelopmental markers in neuroleptic-naïve, recent-onset schizophrenia (NRS) subjects in comparison to healthy control (HC) subjects, in order to explore the predictive validity of this composite endophenotype. We administered the Modified Waldrop Scale (MWS) and the Neurological Evaluation Scale(NES) to evaluate MPA and NSS respectively in 40 NRS and 30 matched HC subjects. NRS subjects had significantly higher frequencies of MPAs and NSS than HC. MPA total scores were correlated with greater severity of illness, whereas NES scores did not show any relationship with clinical variables. NRS and HC subjects were most accurately classified (82.9%) when MPA and NSS were considered as a composite phenotype rather than independently. MPA and NSS constitute independent neurodevelopmental markers of schizophrenia and would afford greater predictive validity when used as a composite endophenotype in genetic association studies.

Keywords

schizophrenia; neuroleptic-naïve; MPA; NSS; endophenotype; neurodevelopmental

1. Introduction

The diagnosis of schizophrenia as per current classificatory systems rests primarily on criterion-based identification of the syndromal phenotype depending upon the presence or absence of a heterogeneous group of symptoms. However, this symptom-based characterization of schizophrenia has been found to be inadequate to delineate the underlying neurobiological substrate of this complex disorder, and therefore researchers have recently turned their attention to identifying a more composite phenotype (1) incorporating neuroanatomical, soft neurological, neuropsychological, electrophysiological, brain morphometric and other biological indices that are reliably associated with this condition. Study of these endophenotypes (2) is expected to facilitate unraveling of the molecular genetic mechanisms underlying this complex and enigmatic condition.

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Schizophrenia is conceptualized as a neurodevelopmental disorder (3) with manifest anomalies of peripheral ectodermal structures that are formed simultaneously with the cerebral cortex during intra-uterine development. The presence of such minor physical anomalies (MPAs) is suggested to be a very important indirect evidence for cerebral maldevelopment in schizophrenia (4). The generalized neurodevelopmental deficit underlying schizophrenia may also be manifested as subtle, nonspecific and non-localizable neurological signs, referred to as neurological soft signs (NSS) (5).

MPAs, specifically craniofacial anomalies, have been shown to be significantly higher in schizophrenia subjects (6,7) but not in mood disordered patients (7) when compared to controls. The parents (1) and siblings (8) of schizophrenia subjects were also found to have significantly higher MPA scores than controls.

NSS serve as indicators of subtle neural circuit dysfunction underlying a variety of neuropsychiatric conditions including schizophrenia (5,9,10). Keshavan et al.(11) found abnormalities of cognitive/perceptual tasks in neuroleptic-naïve schizophrenia patients that distinguished them from those with non-schizophrenia psychoses and healthy controls. Study of NSS in patients presenting in the first episode of their illness before exposure to neuroleptics has the advantage of avoiding confounding factors such as variable duration of illness, and exposure to psychotropic agents.

MPA and NSS in combination may prove to be a more robust endophenotype of schizophrenia, providing a quantitative evaluation of what was previously described as schizotaxia by Meehl (12). A composite phenotypical study incorporating MPA and NSS with a view to studying their inter-relationships, their possible association with psychopathology, along with their combined diagnostic utility has not so far been carried out in neuroleptic-naïve, recent-onset schizophrenia (NRS) patients, and therefore constituted the aim of the present study, carried out in NRS patients. We hypothesized that schizophrenia subjects would have higher frequencies of both MPA and NSS and that these variables in combination would discriminate schizophrenia from healthy subjects better than what each variable does independently.

2. Methods

The study had the approval of the Institute Ethics Committee of the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. Written informed consent was obtained from the all the subjects (and their legally qualified representatives in case of patients) prior to enrollment into the study.

2.1 Subjects

2.1.1 Patients—Forty NRS patients were recruited into the study by purposive sampling, from those who attended the outpatient services of NIMHANS. None of the subjects recruited into the study dropped out prior to assessments. The inclusion criteria were: a DSM-IV diagnosis of schizophrenia, right-handedness, duration from onset of illness ≤ 5 years and age between 17-50 years. The diagnosis of schizophrenia was arrived at using criteria from the Diagnostic and Statistical Manual for Mental Disorders-Fourth edition (DSM-IV) (13) based on the consensus of a research psychiatrist who conducted a semi-structured interview and a trained research assistant who used the Mini International Neuropsychiatric Interview (MINI) (14) Plus. These research associates were not involved in ratings of psychopathology, MPA or NSS. The exclusion criteria included previous exposure to psychotropic drugs; significant suicidal or homicidal risk or other disruptive behaviour which warranted immediate interventions and history of ECT within the previous 6 months.

2.1.2 Controls—Thirty healthy individuals in the same age group as the patients (17-50 years) were recruited by word of mouth. These subjects, predominantly constituted by hospital staff and bystanders of hospitalized patients, were interviewed by a trained research assistant using MINI-Plus and ascertained to have no present or past neuropsychiatric disorders; in addition, there was no history of psychotic disorders in their first degree relatives, as ascertained using an unstructured clinical interview of the recruited subjects.

2.2 Clinical assessments

Handedness was assessed using Edinburgh Handedness Inventory (15). The baseline schizophrenia psychopathology severity was evaluated by administering the Positive and Negative Syndrome Scale (PANSS) (16) by two trained raters (B.R. and V. A.) who had established good inter-rater reliability (ICC) [ICC for: PANSS positive symptom subscale=0.87; negative symptom subscale=0.92; general psychopathology subscale=0.85; total score=0.84]. Overall clinical status was assessed using Clinical Global Impression-Severity (CGI-S) (17). The psychopathology and CGI-S ratings were carried out during the initial week following recruitment, subsequent to the MPA and NSS ratings, which were carried out on the same day or the next day following recruitment. The demographic and clinical characteristics of the participants are shown in Table 1.

2.3 Assessment of MPA and NSS

A Modified Waldrop Scale (MWS) (18,19) was used for assessment of MPA. This scale assesses 12 MPA located in the eyes, ears, oral cavity, hands and feet (Table 3). The individual items were scored (from 0-2 for most items and from 0-1 for some items) referring to the descriptive anchors provided (19).

The NSS were evaluated using modified version of the Neurological Evaluation Scale (NES) (5,11), which is the most widely used instrument for assessing neurological deficits in schizophrenia. NES consists of 30 items, presented in a fixed order. The items are scored with reference to the descriptive anchors provided, on a three-point scale (no abnormality=0; mild, but definite impairment=1; marked impairment=2) with the exception of “suck” and “snout” reflexes which are scored 0 or 2. For the items measured bilaterally, the higher of the two ratings was included in the analysis. The scale comprises of the following conceptually-derived subscales: sensory integration, motor coordination and sequencing of complex motor task (5).

The assessments were carried out by trained raters (B.R. and V.A.) who established good inter-rater reliability for the MPA (ICC=0.98) and NES (ICC=0.93) in a sample of 10 schizophrenia subjects and 10 healthy subjects prior to carrying out the assessments on the study sample. These raters, trained in assessment of MPA, NSS and psychopathology, were medical graduates without post-graduate training in psychiatry. Further, these raters were not involved in diagnosis and recruitment of subjects, nor were they aware of the specific research hypotheses. Further the raters periodically conducted assessments together in the presence of an experienced psychiatrist (J.P.J.) to avoid rater drift.

2.4 Statistical analyses

Parametric and non-parametric statistical tests were used for normally and non-normally distributed variables respectively. The frequencies of the MWS items were compared across schizophrenia and control subjects using χ^2 statistic. Group comparisons of MWS and NES total scores were carried out using Mann-Whitney U test. Normally distributed psychopathology scores were compared across the MPA subgroups (no MPAs vs 1 MPA or more) using independent samples t-test. Correlation between neurodevelopmental and clinical/sociodemographic variables was assessed using using Kendall’s tau_b. Finally, a step-by-step

linear discriminant functional analysis was carried out to predict group membership (schizophrenia, controls) based on the predictor variables, i.e., MWS and NES total scores. The statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 11.5.

3. Results

The NRS and HC groups were comparable on most sociodemographic variables (Table 1). No significant gender differences were noted on MWS scores in both NRS (Mann-Whitney U=194.00, df=1, p< 0.978) and HC (Mann-Whitney U=85.00, df=1, p<0.530) groups. However, while the HC did not show gender differences in the NES scores (Mann-Whitney U=98.00, df=1, p<0.948), female NRS subjects had significantly higher NES scores when compared to male NRS subjects (Mann-Whitney U=92.00, df=1, p<0.004).

NRS subjects had significantly higher total MWS and NES scores when compared to HC (Table 2). Table 3 shows the comparisons between NRS and HC groups in the frequencies of the 12 MPAs assessed. The most frequent MPA noted in HC was furrowed tongue whereas in the NRS group, the most commonly noted MPA was abnormalities of the palate. The proportion of subjects with adherent earlobes, palatal abnormalities and gap between 1^{st} and 2^{nd} toes was significantly higher in the NRS group when compared to HC.

Thirty eight out of the 40 NRS subjects (95%) had at least one NSS, whereas only 7 out of the 30 HC (23.33%) had a minimum of one NSS. NRS subjects had a mean total NES score of 10.68 (s.d=6.74; range: 0-26), whereas the mean total NES score of HC was only 1.53 (s.d.=3.71; range: 0-16). The comparative performances of NRS subjects and HC on the NES are given in Table 4. NRS subjects had significantly higher scores than HC on sensory integration (audiovisual integration, stereognosis, graphaesthesia, extinction and right-left confusion) (Mann-Whitney U=176.50, df=1, p<0.000), motor coordination (rapid alternating movements, tandem walk, finger-thumb opposition and finger-to-nose test) (Mann-Whitney U=180.00, df=1, p<0.000) and sequencing of complex motor tasks (fist-ring test, fist-edge-palm test, Ozeretski test, rhythm tapping reproduction and rhythm tapping production) (Mann-Whitney U=216.50, df=1, p<0.000).

On dividing the NRS and HC samples into subsamples with no MPAs and with 1 or more MPAs, and then comparing the NES scores across these sub-samples, no significant difference in NES scores were noted in the schizophrenia group (Table 5). No significant differences in the NES sub-scores were noted among NRS and HC across sub-samples with no MPAs vs those with 1 or more MPAs. Comparing psychopathology indices across the NRS subsamples with no MPAs (n=11) and with 1 or more MPAs (n=29), it was found that the second subgroup had significantly higher positive symptoms (t=-2.393; p<0.025), negative symptoms (t=-2.282; p<0.028), general psychopathology (t=-4.080; p<0.000), total PANSS scores (t=-4.283; p<0.000) and CGI severity (Mann-Whitney U=94, df=1, p<0.048).

Considering that there were only two NRS subjects with no NSS, the schizophrenia sample was divided into two groups based on the median NES total score in schizophrenia subjects [group 1: those with NES total scores ≤ 12 (n=21); group 2: those with NES total scores > 12 (n=19)]. Comparison of MWS total scores between these two sub-groups did not reveal any significant differences (Mann-Whitney U=195.500, df=1, p<0.915). Further, comparison of clinical and socio-demographical variables between these two sub-groups also did not reveal any significant differences.

Correlational analyses using Kendall's tau_b revealed significant positive relationship between MWS total scores and the NES total scores (Kendall's tau_b =0.345; p<0.000) in the combined sample (schizophrenia and controls) and in controls (Kendall's tau_b =0.367; p<0.029),

whereas there was no significant correlation noted in the schizophrenia sample (Kendall's tau_b =0.065; p<0.591). Significant positive correlation was noted between MWS total score and PANSS total (Kendall's tau_b =0.377; p<0.002), positive (Kendall's tau_b=0.360; p<0.003) and general psychopathology (Kendall's tau_b =0.333; p<0.006) subscores but not with negative subscore (Kendall's tau_b =0.116; p<0.339). Significant positive correlation was also noted between MWS scores and CGI-S (Kendall's tau_b =0.405; p<0.004),. In sharp contrast to the above, no significant correlation was noted between NES total scores and any of the psychopathology indices (PANSS, CGI-S). Further, no significant correlation was noted between age at onset of schizophrenia with MWS total scores (of the whole schizophrenia sample as well as separately for males and females), NES total scores, PANSS total scores and subscores, and CGI-S scores.

A step-by-step linear discriminant function analysis accurately classified 82.9% of the original 70 cases (77.5% of the NRS subjects and 90% of the HC subjects) (Wilks' λ=0.561; χ^2 =38.68; df=2; p<0.000) on the basis of the MWS and NES total scores entered stepwise using the Wilk's lambda method with F-values of 3.84 and 2.71 as criteria for entry and removal respectively. When MWS total score was entered independently in a separate discriminant function analysis, only 65.7% of the original cases (72.5% of the NRS subjects and 56.7% of the HC subjects) were correctly classified. Similarly, when NES total scored was entered independently in the discriminant function analysis, only 74.3% of the original cases (65% of the NRS subjects and 86.7% of the HC subjects) were correctly classified.

4. Discussion

Our findings highlight the utility of considering MPA and NSS as a composite endophenotype in NRS patients. The MPA and NSS findings replicate those of previous studies in chronic medicated (1,7,20), recent-onset, medicated (21,22,23) and recent-onset drug-naïve schizophrenia subjects (24). Most of these studies have not evaluated MPA and NSS in the same sample. The few studies that have evaluated both MPA and NSS simultaneously have reported their findings on chronic and or medicated schizophrenia patients (1,22). It has been shown that NSS are twice as likely to be present in medicated schizophrenia patients as compared to neuroleptic-naïve patients, even though neuroleptic-naïve patients still had significantly greater severity of NSS when compared to healthy controls (10). This highlights the need to study these neurodevelopmental markers by avoiding the confounding effects of medications to understand the pathophysiology of schizophrenia better. To the best of our knowledge, no previous study has attempted to explore the utility of MPA and NSS in combination as a composite endophenotype of schizophrenia in NRS patients.

4.1 Minor Physical Anomalies

Our finding of NRS patients having significantly higher MWS scores as compared to HC is replicative of previous studies (review, 25). Specifically, patients had significantly higher frequencies of adherent ear lobes, palatal abnormalities and gap between 1st and 2nd toes. The other MPAs included in the scale, with the exception of furrowed tongue were rather rare in both groups to be of any value in discriminating between the groups. The most common MPA observed in HC was furrowed tongue; the frequency of this MPA in HC almost equaled the frequency in NRS subjects (Table 3). The finding of palatal abnormalities being the most common MPA in schizophrenia subjects replicates earlier reports (19,20). There were no gender differences in the frequencies of MPA in keeping with the findings of McGrath et al. (19) and Green et al. (20).

4.2 Neurological Soft Signs

NRS patients showed impairment on almost all items that test sensory integration, motor coordination and sequencing of complex motor tasks (Table 4). Overall, our results concur with those of previous studies that have demonstrated a higher prevalence of NSS in schizophrenia subjects, providing further support to the notion that NSS are indicators of an underlying genetically transmitted vulnerability trait factor of schizophrenia or more broadly for psychoses in general (26,27).

The finding of female schizophrenia patients having significantly higher NES total scores when compared to male schizophrenia patients is replicative of Gourion et al. (1)'s observation. It must be noted, however, that female schizophrenia subjects had a significantly lower level of educational status when compared to males (χ^2=10.022, df=2, p<0.007), while this gender difference in educational status was not present in control subjects (χ^2=3.635, df=2, p<0.162). Interestingly, educational status was significantly negatively correlated with NES scores only in schizophrenia subjects (Kendall's tau_b=-0.357, p<0.006). Since it has been observed by most previous studies that there are no gender differences in NSS (review, 28), the lower educational status of female schizophrenia subjects may explain our finding.

4.3 Relationship between MPA and NSS

Replicating the findings of Gourion et al. (1), correlational analysis revealed a significant positive relationship between MWS and NES total scores in the combined sample (schizophrenia+control). However, a causal relationship, in terms of NSS being the result of MPA was ruled out, since there were no group differences noted on NES scores between sub-groups with no MPAs vs 1 or more MPAs in the schizophrenia and control groups. Additionally, there were no differences in MWS scores between the subgroups with NES score >12 vs those with NES score ≤ 12 in schizophrenia subjects. The fact that the MPA-NSS correlation was not significant in the schizophrenia subjects lends further credence to the lack of evidence for causality. Thus, it may be inferred that MPA and NSS constitute independent vulnerability trait indices for schizophrenia, which justifies inclusion of both in an extended phenotypic characterization of schizophrenia (1).

4.4 Relationship between MPA/NSS with psychopathology

MWS total scores were significantly positively correlated with PANSS total scores and sub-scores as well as CGI-severity scores, indicating that presence of MPAs portends a greater severity of illness in schizophrenia subjects. In contrast to the above NSS did not show significant correlation with psychopathology indices. Sub-group comparisons further revealed that schizophrenia subjects with 1 or more MPAs had greater positive symptoms, negative symptoms, general psychopathology, as well as overall severity of psychopathology as indicated by greater PANSS total scores and CGI-severity scores. Sub-group comparisons based on NES total scores did not reveal any significant relationship between NSS and clinical or socio-demographic variables.

The putative association between NSS and psychopathological indices has been a controversial topic, owing to inconsistent reports in the literature (26). Our results, which indicate a remarkable lack of association between NSS and psychopathological variables are in agreement with those of Buchanan et al. (29) and Bartko et al. (30), while contrasting with studies that have shown such an association in the acute phase (31), subacute phase (26) and during one year follow-up assessments (21). It is to be noted that a cross-sectional examination of the relationship between NSS and psychopathology will be influenced by factors such as the variability in the phase of illness of subjects in the study sample (acute vs subacute vs chronic) (26) as well as neuroleptic drug treatment (10,32). Our sample which comprised of neuroleptic-naïve schizophrenia subjects had a considerable variability in their duration of

untreated psychosis (19.83 ± 14.24; range: 3-60 months), suggesting that patients may have been in different phases of the disorder at the point of assessment.

Thus it may be inferred that MPA constitutes a neurodevelopmental marker that predicts a greater severity of illness, whereas NSS constitutes a robust trait marker of schizophrenia independent of MPA, but which possibly reflects one of the main characteristics of schizophrenic psychoses i.e., their fluctuating course.

4.5 Diagnostic utility and validity of the MPA/NSS composite phenotype

NRS patients and HC were most accurately classified (82.9%) when MPA and NSS were considered as a composite phenotype rather than independently. The accuracy of classification was lowest (65.7%), when MWS total score was used as the lone predictor variable, while NES total score as the lone predictor variable gave intermediate results (74.3%). Gourion et al. (1) showed that MPA and NSS as a composite phenotype was useful in accurately classifying non-psychotic parents of schizophrenia subjects as presumed carriers or presumed non-carriers. These authors recommend the co-assessment of these two neurodevelopmental markers to represent a composite phenotypical extension of schizophrenia, consistent with genetic liability (MPA: 33; NSS: review, 34). NSS, however, have been demonstrated in other neuropsychiatric conditions such as bipolar disorder, unipolar depression, OCD etc. (35,36) and therefore may constitute a general trait vulnerability index for various neuropsychiatric conditions, unlike MPA, which seem to be more specific to schizophrenia. Nonetheless, the results of our study clearly demonstrate the utility of these neurodevelopmental markers in combination in reliably classifying and differentiating NRS from HC subjects.

4.6 Advantages and limitations

We studied neuroleptic-naïve, recent-onset schizophrenia subjects thereby avoiding the confounding effects of medications and chronicity on neurodevelopmental markers, especially the NSS (10). The patient group and control groups did not differ in their age, educational status and gender distribution, thereby ruling out the effects of these variables on the group comparisons (1,37). However, female NRS subjects had a significantly lower level of education when compared to males; this could have had a confounding effect on gender-wise disparity of NES scores in the NRS sample. The shorter version of the original Waldrop scale (MWS, 19) was used in the present study, keeping in mind the uncertainty regarding the validity of certain of the original Waldrop items (e.g., head circumference, hair quality, hypertelorism etc.). We felt that this shorter scale could promote ease of administration of the most frequently observed MPAs with proven validity. It is striking to note that, even in a limited sample of NRS subjects who were evaluated in this study, marked differences in the frequencies of MPAs and NSS were observed, which in turn were shown to accurately distinguish NRS patients from HC. The assessment of MPAs and NSS was conducted by researchers who were not blind to the patient vs non-patient status of the subjects, as is the case in almost all such previous studies (1,6,8,19,21,22). Even in a previous study which attempted blinding (11), the blinding was only with regard to the consensus research diagnosis, while the raters were reported to have been aware of the patients' symptoms at the time of rating. In view of complete blinding being difficult to strictly accomplish in such studies, all attempts were made, as detailed in the methods section, to ensure that the ratings were as reliably done as possible.

4.7 Implications for genetic studies of schizophrenia

Our results highlight the utility of a composite evaluation of MPA and NSS in expanding the schizophrenia phenotype. Both these neurodevelopmental markers meet the criteria for endophenotypes (2) for schizophrenia in that they have been shown to be i) associated with the illness in the population (6,7,9,10,11); ii) heritable (1,38); iii) stable (21,29); iv) manifest in the various phases of the illness (21,26,31); v) co-segregating with the illness in families

(8,22,39); and vi) present in non-affected family members at a higher rate than general population (1). Molecular genetic approaches employing a QTL perspective, could hopefully link these endophenotypes with allelic variations on candidate genes of interest, such as fibroblast growth factor receptor (FGFR) genotypes 1, 2 and 3 in case of MPA (40) and apolipoprotein E (apoE) ε4 genotype in the case of NSS (41). This composite endophenotype could even be further refined by combining other neurobiological indices that are linked to these neurodevelopmental markers such as brain morphometry (42,43) and neurocognitive deficits (44,45) , thereby resulting in a much "cleaner" endophenotype for genetic studies. This approach involving refinement of the schizophrenia phenotype by including neurodevelopmental markers along with other endophenotypes that are closer to the primary effects of susceptibility genes than are clinical symptoms (2,46) offers hope for tracking the multiple genes of small effect conferring vulnerability for development of complex disorders such as schizophrenia.

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Table 1

Sociodemographic and illness characteristics of the study samples

Socio-demographic and illness characteristics	Subjects (N=70)	
	Schizophrenia [n=40 (57.14%)]	**Controls [n=30 (42.86%)]**
Gender		
Male	23 (57.5%)	20 (66.7%)
Female	17 (42.5%)	10 (33.3%)
Age (years)	30.03 ± 6.02 (19-45)	30.77 ± 7.62 (19-50)
Education		
Illiterate/ Primary education	19 (47.5%)	14 (46.6%)
Secondary/Pre-university	17 (42.5%)	13 (43.4%)
Graduate/Post-graduate	4 (10%)	3 (10%)
Domicile		
Urban	7 (17.5%)	30 (100%)
Rural	33 (84.6%)	0 (0%)
Diagnosis		
Paranoid schizophrenia	26 (65%)	NA
Undifferentiated schizophrenia	10 (25%)	
Schizophreniform disorder	4 (10%)	
Age of onset of illness (years)	28.53 ± 6.13 (17-43)	NA
Duration of illness (months)	19.83 ± 14.24 (3-60)	NA

Table 2

Comparison of total MWS and NES scores between schizophrenia subjects and healthy controls

	GROUP	Mean Rank/Sum of ranks	Mann-Whitney U	Asymptotic sig (2-tailed)
MWS-total scores	Schizophrenia (n=40)	42.29 / 1691.50	328.50	0.001
	Controls (n=30)	26.45 / 793.50		
NES-total scores	Schizophrenia (n=40)	47.70 / 1908.00	112.00	0.000
	Controls (n=30)	19.23 / 577.00		

Table 3

Comparison of the frequencies of the 12 MPAs between schizophrenia subjects and healthy controls

MPAs	Schizophrenia (n=40)	Controls (n=30)	Pearson Chi-square test; asymptotic sig (2-sided)
Epicanthus	0 (0%)	0 (0%)	-
Low set ears	2 (5 %)	0 (0%)	NS
Adherent earlobes	10 (25%)	2 (6.7%)	χ^2= 4.05, df=1, p<0.044
Malformed ears	3 (7.5%)	0 (0%)	NS
Asymmetrical ears	1 (2.5%)	0 (0%)	NS
Palate	20 (50%)	0 (0%)	χ^2= 21.00, df=1, p < 0.000
Tongue	17 (42.5%)	13 (43.3%)	NS
Curved 5th finger	5 (12.5%)	0 (0%)	NS
Transverse palmar crease	0 (0%)	0 (0%)	-
Third toe	1 (2.5%)	1 (3.3%)	NS
Syndactylia	1 (2.5%)	0 (0%)	NS
Gap between 1st and 2nd toes	16 (40%)	3 (10%)	χ^2= 7.80, df=1, p < 0.005

Table 4

Comparison of the performance* on NES# between schizophrenia subjects and healthy controls

NES items	Schizophrenia (n=40)	Controls (n=30)	Chi-square test; df; sig (2-sided)
Sensory integration			
Audiovisual integration			
No errors	20 (50%)	27 (90%)	χ^2 =12.433; df=1; p <0.000
1 or more errors	20 (50%)	3 (10%)	
Stereognosis			
No errors	25 (62.5%)	30 (100%)	χ^2 =14.318; df=1; p <0.000
1 or more errors	15 (37.5%)	0 (0%)	
Graphaesthesia			
No errors	8 (20%)	24 (80%)	χ^2 =24.868; df=1; p<0.000
1 or more errors	32 (80%)	6(20%)	
Extinction: face-hand test			
No errors	29 (72.5%)	29 (96.7%)	χ^2 =7.049; df=1; p <0.008
1 or more errors	11 (27.5%)	1 (3.3%)	
Right-left confusion			
No errors	27 (67.5%)	28 (93.3%)	χ^2 =6.795; df=1; p<0.009
1 or more errors	13 (32.5%)	2 (6.7%)	
Motor co-ordination			
Rapid alternating movements			
No major disruption	24 (60%)	30 (100%)	χ^2 =15.556; df=1; p <0.000
≥3 hesitations/major disruption	16 (40%)	0 (0%)	
Tandem walk			
No missteps	27 (67.5%)	30 (100%)	χ^2 =11.974; df=1; p<0.001
1or more missteps	13 (32.5%)	0 (0%)	
Finger-thumb opposition			
No major disruption	26 (65%)	30 (100%)	χ^2 =13.125; df=1; Fisher's exact sig (2-sided) <0.000
2-3 mistakes/major disruption	14 (35%)	0 (0%)	
Finger-to-nose test			
No intention tremor or past pointing	27 (67.5%)	30 (100%)	χ^2 =11.974; df=1; Fisher's exact sig (2-sided) <0.001
Mild/marked intention tremor or past pointing	13 (32.5%)	0 (0%)	
Sequencing of complex motor acts			
Fist-ring test			
No major disruption	12 (30%)	24 (80%)	χ^2 =17.157; df=1; p <0.000
2-4 hesitation errors/major disruption	28 (70%)	6 (20%)	
Fist-edge-palm test			
No major disruption	17 (42.5%)	27 (90%)	χ^2 =16.567; df=1; p<0.000
2-4 hesitation errors/major disruption	23 (57.5%)	3 (10%)	
Ozeretski test			
No major disruption	20 (50%)	27 (90%)	χ^2 =12.433; df=1; p <0.000
2-4 hesitation errors/major disruption	20 (50%)	3 (10%)	
Rhythm tapping-reproduction			
No errors	16 (40%)	26 (86.7%)	χ^2 =15.556; df=1; p<0.000
≥ 1 error	24 (60%)	4 (13.3%)	
Rhythm tapping-production			
No errors	20 (50%)	27 (90%)	χ^2 =12.433; df=1; p <0.000
≥ 1 error	20 (50%)	3 (10%)	
Other tests			
Adventitious overflow			
Absent	38 (97.4%)	30 (100%)	NS
Irregular fluttering movt of fingers	1 (2.6%)	0 (0%)	
Romberg test			
Stable	28 (70%)	30 (100%)	χ^2 =10.862; df=1; p<0.001
Marked swaying/steps to maintain balance	12 (30%)	0 (0%)	

NES items	Schizophrenia (n=40)	Controls (n=30)	Chi-square test; df; sig (2-sided)
Tremor			
No tremor	33 (82.5%)	30 (100%)	χ^2=5.833; df=1; p <0.016; Fisher's exact significance (2-sided) <0.017
Mild fine tremor	7 (17.5%)	0 (0%)	
Memory			
Rememgers all words	12 (30%)	27 (90%)	χ^2 =25.012; df=1; p <0.000
≤ 3 words	28 (70%)	3 (10%)	
Mirror movements			
No observable movts	36 (90%)	28 (93.3%)	NS
Minor inconsistent movts	4 (10%)	2 (6.7%)	
Synkinesis			
No movt of head	35 (89.7%)	30 (100%)	χ^2=4.038; df=1; p <0.044; Fisher's exact significance (2-sided) <0.066
Movt on 1st trial/ even when told to keep still	5 (7.7%)	0 (0%)	
Convergence			
Eyes converge on objects	39 (97.5%)	30 (100%)	NS
1 or both eyes are unable to converge	1 (2.5%)	0 (0%)	
Gaze impersistence			
No deviation	28 (70%)	30 (100%)	χ^2 =10.862; df=1; p<0.001
Deviation before/after 20s	12 (30%)	0 (0%)	
Glabellar reflex			
3 or fewer blinks	29 (72.5%)	29 (96.7%)	χ^2 =7.049; df=1; p <0.008
≥ 4 full blinks	11 (27.5%)	1 (3.3%)	
Snout reflex			
No contraction of orbicularis oculi	40 (100%)	30 (100%)	NS
Any contraction	0 (0%)	0 (0%)	
Grasp reflex			
No flexion of finger	40 (100%)	30 (100%)	NS
Mild/marked flexion	0 (0%)	0 (0%)	
Suck reflex			
No movement	40 (100%)	30 (100%)	NS
Any pursing/sucking movement	0 (0%)	0 (0%)	
Palmomental reflex			
Absent	40 (100%)	30 (100%)	NS
Present	0 (0%)	0 (0%)	

*Ratings 1 and 2 for all items were collapsed into a single score for purpose of statistical analysis

#excluding items measuring cerebral dominance

Table 5

Comparison of NES scores between MPA subgroups (No MPAs vs 1 or more MPAs) in schizophrenia subjects and healthy controls

	Schizophrenia (N=40)		Healthy Controls (N=30)	
	No MPAs (n=11)	**1 or more MPAs (n=29)**	**No MPAs (n=17)**	**1 or more MPAs (n=13)**
NES scores: Mean rank / Sum of ranks	17.55 / 193.00	21.62 / 627.00	13.82 / 235.00	17.69 / 230.00
Mann-Whitney U	127.00		82.00	
Asymptotic sig (2-tailed)	0.338		0.245	