Neurological Soft Signs in schizophrenia and mood disorders: Investigating a potential endophenotype
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NEUROLOGICAL SOFT SIGNS IN SCHIZOPHRENIA AND MOOD DISORDERS: INVESTIGATING A POTENTIAL ENDOPHENOTYPE.

Proefschrift

ter verkrijging van het doctoraat in de Medische Wetenschappen aan de Rijksuniversiteit Groningen op gezag van de Rector Magnificus, dr F. Zwarts, in het openbaar te verdedigen op woensdag 28 september 2005 om 14:45 uur

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Marco Paul Maria Boks
geboren op 21 augustus 1966
te Amerongen
Promotor: Prof. Dr. R.J. van den Bosch
Copromotor: Dr. R. Kneegtering
Beoordelingscommissie: Prof. Dr. R.S. Kahn
                      Prof. Dr. W. Nolen
                      Prof. Dr. G. ter Horst
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CHAPTER 1
INTRODUCTION
BACKGROUND

Ever since the introduction of the diagnosis of dementia-praecox by Kreapelin and the name schizophrenia in a later stage by Bleuler, there has been the notion of certain physical abnormalities that are associated with this diagnosis. Kraepelin wrote: ‘Ausser den psychisen Storungen sind auch auf Korperlichem Gebiete eine Reihe von Krankheitserscheinungen zu verzeichen, deren genauere Beziehungen zu dem grundleiden allerdings noch nicht in allen Punkten feststehen’ (‘Besides the psychic disorder there are also in the physical domain a series of morbid phenomena to record, whose exact relations to the fundamental malady are not yet proved in all points’ (E. Kraepelin, Psychiatrie; Ein lehrbuch fur studirende und aerzte, 1899 Leipzig). One of these phenomena includes subtle motor abnormalities. This concept was further embraced by child and adolescent psychiatry and the concept of “woodteriness” and clumsiness led to extensive research into this phenomenon in the 1960’s. In the early days of this research evidence was found for an association of early disturbances in motor development with schizophrenia (Fish and Hagin 1972;Fish 1977). However, the aetiology of these abnormalities remained poorly understood and was further obscured by the introduction of antipsychotics.

The term neurological soft signs first emerged in around 1975 (Tucker et al. 1975;Quitkin et al. 1976) and was used to reflect the absence of obvious localised neuropathology underlying these signs. In the 1980’s the interest in neurological soft signs (NSS) increased after associations were found with clinical outcome (Torrey 1980) and neuropsychological correlates (Liddle 1987;Manschreck et al. 1982). The interest in NSS surged after it became clear that the prevalence of NSS in relatives of schizophrenia patients was increased (Woods et al. 1986;Kinney et al. 1986) and NSS were hoped to provide a trait marker for schizophrenia. With the increase in quantity, the quality of the research also greatly improved and more systematic and better validated means of assessments were introduced (Buchanan and Heinrichs 1989;Chen et al. 1995). It then emerged that NSS are also present in numerous psychiatric conditions such as alcoholism, bipolar disorder and neuroticism. However, the presence of NSS in other psychiatric disorders does not rule out that specific NSS or groups of NSS do show specificity for a diagnosis of schizophrenia or are related to particular symptoms or symptom dimensions but the diversity of often contradicting studies on NSS using different definitions of signs and categories, in even more diagnostic groups, describing relationships with medication, neuropsychological measures, brain abnormalities, obstetric complications, psychopathology and so on, are indicative of the complexity of the meaning of NSS.

Because NSS incorporate a broad diversity of signs they may well reflect diverse neuropathology and as a consequence emerge in a broad range of conditions. Alternatively they could represent global cerebral dysfunction and thus represent non-specific epiphenomena. Structural and functional brain imaging studies into the localisation of NSS have yielded contradicting results (Rubin et al. 1994;Schroder et al. 1995;Braus et al. 1999;Kolakowska et al. 1985). One fMRI study has implied the involvement of the primary sensory motor area (Schroder et al. 1995) but others have failed to find a localised effect of NSS in the brain (Braus et al. 1999).
functional and structural brain imaging studies are related to the diagnosis of schizophrenia and are almost impossible to separate from the effects of NSS themselves.

**MOVEMENT DISORDERS**

Kraepelin wrote about phenomena in the physical domain, and was one of the firsts to record the movement disorders in psychiatric patients. In fact some early school of psychopathology classified patients with (spontaneous) movement disorders as choreiform (parakinetic) and proposed a distinct neuropathology (Leonhart 1936). Indeed, recent studies have emphasised the relatively high prevalence of spontaneous dyskinesia in schizophrenia (Fenton 2000;Van Os et al. 1997) and the vulnerability to dyskinesia in affective disorder (Kane 1999). Catatonia was originally described in 1873 as part of affective syndrome by Kahlbaum. Kraepelin and Bleuler adopted this to be a part of the schizophrenia syndrome, but later studies have re-established the prevalence of catatonia signs in mood disorders and particularly bipolar disorder (Barnes et al. 1986;Abrams et al. 1979;Taylor and Abrams 1977;Taylor and Abrams 1973). Most NSS assessments included signs that are traditionally in the domain of dyskinesia, extra-pyramidal signs (EPS) and catatonia. In the Cambridge Neurological Investigation (CNI) (Chen et al. 1995) a category for catatonia, tardive dyskinesia and for extra-pyramidal signs is included. However, the similarities between the movement disorders and NSS are not restricted to overlap of signs. In addition there are considerable similarities between movement disorders and NSS and their relationships with other properties of psychiatric disorder such as for instance negative symptoms, cognitive function and age. NSS and TD both are associated with brain abnormalities such as increased ventricle to brain ratio (Hoffman and Casey 1991;Rubin et al. 1994;DeMyer et al. 1988) and with neuropsychological abnormalities such as memory impairment (Krabbendam et al. 2000;Liddle 1987;Flashman et al. 1996). Our knowledge on movement disorders has increased considerably, and the involvement of the basal ganglia in their aetiology is now undisputed. However the primary process of spontaneous movement disorders in schizophrenia and mood disorders is still obscured and investigating some of the complex relationship between NSS and movement disorders could therefore contribute to our understanding of both NSS and movement disorders.

**ENDOPHENOTYPES**

When it became apparent that the majority of studies did not find a correlation of NSS with clinical outcome and the specificity of NSS for schizophrenia appeared to be low the usefulness of NSS as a clinical tool seemed limited and as a consequence interest waned. However with the increased attention for psychiatric genetics attention re-emerged. An increase in NSS has been established in siblings of schizophrenia patients (Ismail et al. 1998;Cantor-Graae E. et al. 2000), and also schizophrenia patients with a family history of psychosis (Woods et al. 1991) show increased numbers of NSS compared to those patients with a negative family history. This suggests that increased NSS reflect a genetic vulnerability to schizophrenia and as a consequence could be helpful in the identification of those subjects that are at risk for schizophrenia. The presence of NSS in mood disorders is not necessarily contradicting this as recent studies point towards a shared genetic vulnerability for schizophrenia and mood disorders.
Introduction

disorders (Maier et al. 1993). Moreover, recent studies demonstrate similar genetic expression in bipolar mood disorders and schizophrenia of homeobox genes (Kromkamp et al. 2003) and lipid and myelin-related genes (Tkachev et al. 2003). Furthermore there is evidence of an overlap in chromosomal regions with susceptibility genes for both bipolar disorder and schizophrenia (Berrettini 2000). This is not surprising considering that the majority of symptoms in psychiatric disorders are not limited to one diagnosis alone. Mood symptoms are highly prevalent in psychotic illnesses (Wassink et al. 1999), as are psychotic symptoms in mood disorders (Frances et al. 1981). Therefore if NSS are the reflection of a genetic vulnerability to schizophrenia it would be expected that patients with a mood disorder (who have a higher genetic vulnerability to schizophrenia) also show increased numbers of NSS. Data from family, twin, and adoption studies unequivocally demonstrate the involvement of genetic factors in the transmission of vulnerability to schizophrenia. Scientists expect that identification of genes conferring vulnerability to schizophrenia, and the brain proteins they code for will make it possible to develop better diagnostic procedures, treatments, and preventive interventions targeted at the underlying illness process. However to date there has been only limited progress. As a result of this and the polygenic and quantitative nature of psychiatric disorders the attention in contemporary genetic research has shifted towards endophenotypes to facilitate gene discovery (Egan et al. 2001). Endophenotypes are characteristics that may represent more proximal readout of gene function such as for example neuroimaging findings (Pezawas et al. 2004). Classifying patients based on endophenotype may accelerate the process of gene discovery. Apart from heritable, a good endophenotype should be reliable, measurable and specific for the psychiatric disorder or disorders.

OBJECTIVE

With these studies we aim to investigate the meaning of NSS and its potential as an endophenotype for schizophrenia. We will look at the three requirements for a good endophenotype; measurability, reliability and specificity. We will study the reliability by looking at the interrater reliability (chapter 2) and the test retest reliability by looking at the temporal stability of NSS at two years follow up (chapter 3) and the relationship of NSS with medication by means of a case-control study in a group of first episode schizophrenia patients (chapter 4). We will study the specificity of NSS by means of a literature review (chapter 5) and case-control study in two diagnostic groups (chapter 6). In an attempt to illuminate a potential aetiologi-cal environmental influence on NSS we studied the relationship between NSS and obstetric complications (chapter 7).
Chapter 1

REFERENCES


Introduction


CHAPTER 2
METHOD
SUBJECTS

From 1996 to 2002 all newly admitted patients, aged between 18 and 55, in the department of psychiatry at the University Medical Centre Groningen with a first episode psychosis and all patients admitted with a clinical depression between 1999 and 2001 were asked to participate in this study. After complete description of the study written informed consent was obtained. Healthy volunteers were recruited with several advertisements in local papers. Only volunteers without personal psychiatric history, with a negative psychiatric family history and without current medication were included. Subjects with a score higher than 2 on the General Health Questionnaire (Goldberg and Williams 1988) were also excluded to avoid morbidity in the volunteers. Demographic and clinical characteristics are summarised in table 1 and 2:

Table 1: Demographic variables.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Schizophrenia group</th>
<th>Mood disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>60</td>
<td>217</td>
<td>83</td>
</tr>
<tr>
<td>Mean age (S.D.)</td>
<td>26.9 (8.4)</td>
<td>26.7 (6.4)</td>
<td>33.9 (11.0)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>37 (62)</td>
<td>151 (70)</td>
<td>46 (55)</td>
</tr>
<tr>
<td>Antipsychotics (%)</td>
<td>0 (0)</td>
<td>170 (78)</td>
<td>48 (58)</td>
</tr>
<tr>
<td>Mean dose (S.D.) (haloperidol equivalent)</td>
<td>0 (0)</td>
<td>4.7 (3.6)</td>
<td>2.5 (3.6)</td>
</tr>
<tr>
<td>Antidepressants (%)</td>
<td>0 (0)</td>
<td>21 (10)</td>
<td>44 (53)</td>
</tr>
<tr>
<td>Mood stabilisers (%)</td>
<td>0 (0)</td>
<td>5 (2)</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Neurological history (%)</td>
<td>5 (8.3)</td>
<td>35 (16.2)</td>
<td>22 (28)</td>
</tr>
<tr>
<td>Right handed (%)</td>
<td>51 (85)</td>
<td>192 (890)</td>
<td>73 (88)</td>
</tr>
</tbody>
</table>

Table 2: Diagnosis

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia, undifferentiated type</td>
<td>20</td>
</tr>
<tr>
<td>Schizophrenia, paranoid type</td>
<td>71</td>
</tr>
<tr>
<td>Schizophrenia, disorganised type</td>
<td>5</td>
</tr>
<tr>
<td>Schizophrenia, catatonic type</td>
<td>3</td>
</tr>
<tr>
<td>Schizophreniform disorder</td>
<td>45</td>
</tr>
<tr>
<td>Delusional disorder</td>
<td>8</td>
</tr>
<tr>
<td>Brief psychosis</td>
<td>20</td>
</tr>
<tr>
<td>Psychosis NOS</td>
<td>17</td>
</tr>
<tr>
<td>Schizo-affective disorder</td>
<td>27</td>
</tr>
<tr>
<td>Mood disorders</td>
<td></td>
</tr>
<tr>
<td>Depressive episode</td>
<td>40</td>
</tr>
<tr>
<td>Depressive episode with psychosis</td>
<td>6</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>30</td>
</tr>
<tr>
<td>Mood disorder NOS</td>
<td>5</td>
</tr>
</tbody>
</table>
ASSESSMENTS

- NSS: The subjects were investigated by means of the CNI (Chen et al. 1995) a comprehensive standardised neurological investigation (see chapter 12:appendix). This inventory includes 76 NSS and includes most NSS from the NES (Buchanan and Heinrichs 1989) along with other NSS. We choose this instrument because it was the most comprehensive. In addition to scores at item level it presents 8 categories of NSS; Hard signs, motor coordination, sensory integration, primitive reflexes, tardive dyskinesia, catatonic signs and extra pyramidal signs and suppression failure.
- Diagnosis were made according DSM IV by means of the SCAN interview (Wing et al. 1990).
- Medical history and current complaints were assessed using a semi-structured interview.
- Morbidity of the healthy controls was excluded by means of the General Health Questionnaire (GHQ) (Goldberg and Williams 1988).
- Psychopathology in the schizophrenia patients was assessed by means of the Positive and Negative Symptom Scale (PANSS) (Kay et al. 1987).
- Clinical and demographical data were collected from the case records

INTERRATER RELIABILITY

Four trainees in psychiatry and one neurologist conducted the examinations. Interrater reliability between raters for the total score was assessed in 40 subjects and was good (intraclass correlation = 0.83). Raters were blind to the hypothesis but not to the diagnosis.

The interrater for categories of NSS are summarised in table 3:

<table>
<thead>
<tr>
<th>Category of NSS</th>
<th>Interrater (ICC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesia</td>
<td>0.84</td>
</tr>
<tr>
<td>EPS</td>
<td>0.85</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>0.73</td>
</tr>
<tr>
<td>Suppression failure</td>
<td>0.57</td>
</tr>
<tr>
<td>Hard</td>
<td>0.41</td>
</tr>
<tr>
<td>Primitive reflexes</td>
<td>0.35</td>
</tr>
<tr>
<td>Sensory integration</td>
<td>0.78</td>
</tr>
<tr>
<td>Motor coordination</td>
<td>0.57</td>
</tr>
<tr>
<td>Catatonia</td>
<td>0.55</td>
</tr>
<tr>
<td>Total</td>
<td>0.83</td>
</tr>
</tbody>
</table>

The interrater reliability of NSS assessments is poorly investigated. In the majority of cases there are either measures of reliability for a few, but not all, individual items presented or measures of interrater reliability for categories of signs. With the exception of primitive reflexes and hard signs the interrater reliability was ranging from satisfactory to good. The poor interrater reliability of these categories is likely to be due to the small number of items in these
categories. In the case of primitive reflexes the poor interrater reliability of the sign persistent glabellar reflexes is the result of one of the raters consistently not scoring this sign. It is important to realise the ICC are averaged across raters and are measures for categories of signs. Therefore they may obscure greater inconsistencies at item level. However, bearing in mind the poor interrater reliability of the majority of physical and neurological examinations (Sanders and Keshavan 1998), we believe the assessment to be a useful instrument nevertheless.

FOLLOW UP

A randomised selection of patients was assessed for follow up after 2 year. Patients received a SCAN interview and PANSS and NSS were re-assessed by the main rater (MB) by means of the CNI.

REFERENCES

Wing, J.K., Babor, T., Brugha, T., Burke, J., Cooper, J.E., Giel, R., Jablenski, A., Regier, D., and Sartorius, N., 1990. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry. 47, 589-593.
CHAPTER 3
(revision submitted to European Psychiatry)

THE 2-YEAR STABILITY OF NEUROLOGICAL SOFT SIGNS AFTER A FIRST EPISODE OF NON-AFFECTIVE PSYCHOSIS.

Marco P.M. Boks, Jean-Paul Selten, Stuart Leask, Robert J. van den Bosch.
Chapter 3

ABSTRACT

We examine the 2-year stability of neurological soft signs (NSS) in 29 patients after a first episode of psychosis. The numbers of NSS at inclusion and at 2 years follow-up were similar but there was a significant increase in the numbers of NSS in the sub-group of patients whose dosage of antipsychotic medication had increased over time.

INTRODUCTION

The increased prevalence of neurological soft signs (NSS) in first episode psychosis (Dazzan and Murray 2002) and schizophrenia (Boks et al. 2000; Leask et al. 2002) is well established. An increase in NSS has also been established in the siblings of schizophrenia patients (Ismail et al. 1998; Cantor-Graae E. et al. 2000) and in schizophrenia patients with a family history of psychosis (Woods et al. 1991), leading to the hypothesis that NSS represent a genetic vulnerability to schizophrenia. There has been an ongoing debate about the influence of medication on NSS, with the majority of studies arguing against such an influence. However, to date only four longitudinal studies have been published; Chen et al (2000) followed 43 patients during 5 years, Smith et al (2000) 37 patients with 5 years interval, Torrey (1980) 31 patients with 1 years interval and finally Madsen et al (1999) 18 patients with 5 years interval. All studies but one (Madsen et al. 1999) were conducted in chronically hospitalised schizophrenia patients. Two studies found no major changes in the neurological soft signs at follow up (Torrey 1980; Smith et al. 1999) and one study found an increase of NSS at follow up (Chen et al. 2000). The fourth study also failed to find a significant increase in the number of NSS in the group of schizophrenia patients as a whole at follow up but did find an increase in the number of NSS in the males and in those with high genetic loading, obstetric complications or persistent psychosis (Madsen et al. 1999). We investigated whether the number of NSS increased or remained stable over the two years following a first episode of psychosis. We examined the possible influences of changes in antipsychotic dose and severity of psychopathology on the total number of NSS.

METHOD

All patients admitted at the university hospital Groningen with a first episode of psychosis were asked to participate. After complete description of the study to the patients, written informed consent was obtained. At six weeks NSS were assessed by means of the Cambridge Neurological Inventory (CNI) (Chen et al. 1995), a standardised comprehensive neurological examination. This inventory includes most neurological signs from the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs 1989) along with other neurological signs. DSM IV diagnoses were made using the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al. 1990). Symptoms were assessed by means of the Positive and Negative Symptom Scale (PANSS) (Kay et al. 1987) on the same day as the NSS. After 2 years consecutive patients with a diagnosis in the schizophrenia spectrum were asked for follow up. 29 patients completed the follow up and were included in this study. Previously we reported on the interrater reliabi-
2-year stability

...ility (which was satisfactory, ICC=0.83) and on a significant increase in the number of NSS in patients versus healthy controls at inclusion (Boks et al. 2004).

We examined whether there were significant differences in the numbers of NSS between the first and second assessment using a paired t-test. We calculated the Intra Class Correlation (ICC) as measures of agreement between the first and second rating. We then divided the patients into three groups: PANSS scores increased, unchanged or diminished, and tested any changes in the number of NSS with the Wilcoxon signed rank test. We also divided patients into three groups: medication dosage increased, unchanged and decreased, and again tested any differences in the number of NSS with the Wilcoxon signed rank test. Tests were two-sided, and p-values of 0.05 were considered significant.

RESULTS

Mean age at inclusion was 26.9 years (sd 6.3), 18 patients (62.1%) were male. DSM IV diagnosis at inclusion were; schizophrenia (N=15), schizophreniform disorder (N=7), schizo-affective disorder (N=2), delusional disorder (N=1), psychosis Not Otherwise Specified (N=4). At inclusion 15 patients used atypical antipsychotic drugs and 11 patients classical antipsychotic drugs, 3 patients were medication naive. There were no patients at inclusion or on follow-up who used more than one antipsychotic drug. Chi-square tests showed no significant differences in the ratio of classical and atypical antipsychotic drug, or in the ratio of patients with and without other medication, at inclusion and follow up. Mean dosage in haloperidol equivalents at inclusion was 4.0 (SD 3.0), at follow up 3.8 (SD 3.2).

The total numbers of NSS at inclusion (7.5, SD=7.1) and follow up (8.9, SD=5.5) did not differ significantly (paired t-test, two-sided, t=1.5 p=0.15), and the measures of agreement were substantial (ICC 0.66). There were also no significant changes in the numbers of NSS in the groups based on change in PANSS scores. However we found a significant increase in the number of NSS in the group in which the dosage of antipsychotic medication had increased since inclusion (5.9 (SD 7.1) vs 9.0 (SD 5.2), Wilcoxon signed rank test (Z=2.09, p= 0.036). To investigate the possibility that this was a medication effect we repeated the analysis excluding those signs that may have been influenced by medication ie. all signs from the EPS and TD categories of the CNI (Chen et al. 1995). The results were similar (Wilcoxon signed rank test, Z=2.15, p= 0.032), suggesting that the increase of NSS in this group was not just the side effects of medication.

DISCUSSION

We found no significant changes in the numbers of NSS 2-years after a first episode of psychosis, and the level of agreement between the two assessments was substantial. The number of NSS was increased in patients with an increase of medication, although a decrease in medication had no effect. This group may represent patients with more severe illness who failed to adequately respond to the initial dose. However, since the mean number of NSS at inclusion is slightly lower in this group, this finding could instead represent regression to the mean.
Chapter 3

Strengths of this study include a longitudinal design, inclusion of first episode patients and the relatively low doses of medication. The statistical power is however limited by the sample size. Our results support earlier reports that overall NSS appear to be stable over time, although perhaps not in specific groups.

ACKNOWLEDGEMENT

We are grateful to R. Knegtering, R. Bruggeman, F. Nienhuis and the nursing and medical staff of the psychosis department of the University Medical Centre Groningen, The Netherlands for their support.

REFERENCES

Wing, J.K., Babor, T., Brugha, T., Burke, J., Cooper, J.E., Giel, R., Jablenski, A., Regier, D., Sartorius, N., 1990. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry. 47, 589-593.
THE INFLUENCE OF ANTIPSYCHOTICS ON NEUROLOGICAL SOFT SIGNS AND DYSKINESIA IN FIRST EPISODE PSYCHOSIS.

Marco P.M. Boks, Peter F. Liddle, Sascha Russo, Rikus Knegtering, Robert J. van den Bosch.
Chapter 4

ABSTRACT

First episode psychosis patients on atypical antipsychotics had significantly less dyskinesia signs compared to patients on classical antipsychotics, but no differences regarding the total number of neurological soft signs (NSS). This suggests that antipsychotics do not influence NSS, but it associates atypical antipsychotics with less dyskinesia in the early stages of treatment.

INTRODUCTION

The influence of antipsychotics on neurological soft signs (NSS) in first episode psychosis is still subject to debate (Dazzan and Murray 2002). Particularly the relationship between dyskinesia, extra pyramidal signs (EPS) and NSS. The outcome of any study into the influence of antipsychotics on NSS will to a great extent be determined by the ability of the assessment of NSS to distinguish NSS from EPS and dyskinesia. In addition they should focus on categories of signs in order to enable the discovery of an association between medication and a particular category of NSS. Differences in NSS between patients on atypical and classical antipsychotics could give more insight in the background of evidence (Keefe et al., 1999) suggesting a different profile of atypical antipsychotics, not only regarding EPS and dyskinesia, but also regarding cognitive functions.

METHODS

We examined all admitted patients with a first psychotic episode with a comprehensive standardised neurological examination: the Cambridge Neurological Investigation (CNI) (Chen et al. 1995). The CNI includes EPS and dyskinesia signs. The dyskinesia category consists of nine signs and includes all simple, complex and dyskinetic abnormal involuntary movements in the face trunk and limbs. The EPS category includes increased tone in limbs, decreased associated movements in walking, shuffling gait, arm dropping, tremor and rigidity in the neck. After complete description of the study to the patients, written informed consent was obtained. Patients with a minimum of four weeks on stable medication with no prior medication history and with a diagnosis within the schizophrenia spectrum according to DSM IV were included in this study. Medication dosages were calculated in haloperidol equivalents (Leysen et al. 1998). We compared patients using classical antipsychotics to patients using atypical antipsychotics on ten categories of NSS. We used Mann-Whitney test to compare the groups and corrected for multiple comparison by means of the Bonferroni procedure.

42 patients used atypical antipsychotics (21 risperidone, 18 olanzapine, 1 sertindole, 2 quetiapine). The mean age was 26.3 years (SD 5.9); 67 percent were male; the mean antipsychotic dose in haloperidol equivalents was 4.8 mg (SD 2.0). The mean dose of olanzapine and risperidone in this study was 16.5 mg (SD 22.4) and 2.6 mg (SD 1.1) respectively. The mean duration of antipsychotic treatment was 14 weeks (SD 17.4). 20 patients used classical antipsychotics (4 haloperidol, 10 pimozide, 4 zuclopentixol, 1 flupentixol, 1 fluphenazine). The mean age was 29.2 years (SD 5.9); 70 percent were male; the mean dose in haloperidol equi-
Influence of antipsychotics

valents was 4.8 mg (SD 3.7). The mean duration of antipsychotic treatment was 22 weeks (SD 25.0). In the atypical antipsychotics group, 5 patients (12%) used co-medication (1 on anticholinergics, 3 on benzodiazepines, and 4 on a SSRI). In the classical antipsychotics group 2 patients (10%) used co-medication (1 on anticholinergics and a benzodiazepines, 1 on a tricyclic antidepressant). In the atypical antipsychotics group 21 patients suffered from schizophrenia, 9 patients from schizophreniform disorder, 8 patients from schizo-affective disorder, 1 patient from delusional disorder, 1 patient from brief psychotic disorder and 2 patients from psychosis NOS. In the classical antipsychotics group 11 patients suffered from schizophrenia; 2 patients suffered from schizophreniform disorder, 4 patients from schizo-affective disorder, 2 patient from brief psychotic disorder and 1 patient from psychosis NOS.

All raters received video instruction and 5 training sessions and were blind to any hypothesis. The intrarater reliability across the three raters was assessed in a random sample of 40 cases. The intraclass correlations (ICC) were good; for dyskinesia 0.84, EPS 0.85 and for the total score 0.83. Sex, age and antipsychotics dosage in haloperidol equivalents did not significantly differ between groups.

RESULTS

Table 1 presents the data for NSS for both medication groups. We found significant differences between groups for dyskinesia but not for the overall NSS score.

Table 1: Mean symptom score and test statistics on ten categories of NSS after correction for multiple comparisons.

<table>
<thead>
<tr>
<th>Category of NSS</th>
<th>Atypical antipsychotics Mean score (range) (N=42)</th>
<th>Classical antipsychotics Mean score (range) (N=20)</th>
<th>Mann-Whitney U-test (2-tailed) Z-score p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyskinesia</td>
<td>0.00 (0-0.0)</td>
<td>0.56 (0-5.0)</td>
<td>3.35 0.01*</td>
</tr>
<tr>
<td>Sensory Integration</td>
<td>2.92 (0-9.0)</td>
<td>1.65 (0-6.0)</td>
<td>2.04 NS</td>
</tr>
<tr>
<td>Hard signs</td>
<td>1.00 (0-8.0)</td>
<td>0.35 (0-4.0)</td>
<td>1.27 NS</td>
</tr>
<tr>
<td>Primitive Reflexes</td>
<td>0.00 (0-1.0)</td>
<td>0.10 (0-1.0)</td>
<td>0.45 NS</td>
</tr>
<tr>
<td>EPS</td>
<td>0.85 (0-7.5)</td>
<td>0.77 (0-4.5)</td>
<td>0.31 NS</td>
</tr>
<tr>
<td>Motor coordination</td>
<td>2.55 (0-12.0)</td>
<td>1.78 (0-7.0)</td>
<td>0.21 NS</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1.54 (0-6.0)</td>
<td>1.68 (0-6.5)</td>
<td>0.12 NS</td>
</tr>
<tr>
<td>Suppression Failure</td>
<td>0.90 (0-5.0)</td>
<td>0.72 (0-3.0)</td>
<td>0.07 NS</td>
</tr>
<tr>
<td>Catatonia</td>
<td>0.37 (0-3.5)</td>
<td>0.21 (0-2.0)</td>
<td>0.05 NS</td>
</tr>
<tr>
<td>All signs</td>
<td>10.19 (0-33.0)</td>
<td>7.80 (0-22.0)</td>
<td>0.27 NS</td>
</tr>
</tbody>
</table>

* Significant p<0.05

We found a significant difference in the treatment duration between groups (Mann-Whitney Z= 2.5 p=0.014). Therefore we compared the two groups on the dyskinesia score by means of a univariate analysis of variance with the treatment duration as a co-variate. In the corrected model, the differences regarding dyskinesia remained significant (F=4.2, p= 0.02). To
investigate whether the CNI distinguished NSS from dyskinesia we calculated the correlations between the scores on the NSS categories. There was no correlation between dyskinesia and the total NSS score nor with any specific category of NSS.

**DISCUSSION**

Our study concurs with evidence that antipsychotics do not influence the number of NSS. Moreover it also suggests that atypical antipsychotics are associated with less dyskinesia, even after an average treatment period of 17 weeks and an average age of 27 years. This may indicate that differences in dyskinesia are apparent, shortly after the onset of treatment for a psychotic disorder.

In the absence of a baseline assessment, we cannot exclude the possibility that the groups differed in the severity of movement disorders at baseline. However the apparent low scores on dyskinesia suggest that any dyskinetic signs present were subtle and probably have not influenced treatment selection. Moreover, if there was a systematic effect of pre-existing movement disorder on choice of medication, it would be expected that the prescribing clinician would have selected an atypical antipsychotic for patients with pre-existing movement disorder. Other possible confounders (age, medication dose) did not differ significantly between groups. The influence of co-medication is limited because the majority of patients (89%) did not use co-medication and only one patient in each group used anticholinergics. Although the raters were not blind to the medication, the good interrater reliability reduces the likelihood of assessment bias. The ability of the CNI to distinguish between dyskinesia and NSS was confirmed by the absence of a correlation between the dyskinesia score and any of the specific NSS categories or total NSS score. The low scores on dyskinesia are likely to be related to the short duration of treatment and predominant male sex in our subjects. But above all by the limited sensitivity of the CNI to dyskinesia compared to assessments used in other studies.

Despite its limitations our study suggests a favourable effect of atypical antipsychotics on the level of dyskinesia compared to classical antipsychotics, shortly after the onset of treatment. This would be particularly interesting considering evidence regarding the association of dyskinesia with cognitive impairment in schizophrenia (Pantelis et al. 2001) and evidence that atypical antipsychotics improve cognitive function (Keefe et al. 1999). Therefore further research into the relationship between antipsychotics, dyskinesia and cognition seems warranted.

**ACKNOWLEDGEMENT**

The authors are grateful to Hans den Boer and Richard Bruggeman for helpful comments.
REFERENCES


CHAPTER 5
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THE SPECIFICITY OF NEUROLOGICAL SIGNS IN SCHIZOPHRENIA: A REVIEW.

Marco P.M. Boks, Sascha Russo, Rikus Knegtering, Robert J. van den Bosch.
Chapter 5

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.

There is some evidence that neurological signs correlate with minor neuro-anatomical ab-
normalities (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). Neu-
rological 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 pat-
terns 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 sen-
sory 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;Man-
schreck and Ames 1984) are most impaired in schizophrenia patients.

This review focuses on neurological signs in schizophrenia, mood disorders and healthy sub-
jects. Recent studies emphasise the similarities of neuropathological deviations in schizophr-
enia 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 diag-
nostic 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 where
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 pre-
valence 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.

<table>
<thead>
<tr>
<th>Sign</th>
<th>Schizophrenia</th>
<th>Mood disorders</th>
<th>Normal Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensory integration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extinction</td>
<td>4,6-8,13,15-17</td>
<td>457 (17.4)</td>
<td>28 (0.0)</td>
</tr>
<tr>
<td>L-R disorientation</td>
<td>2-4,6,8-17</td>
<td>861 (27.9)</td>
<td>88 (23.2)</td>
</tr>
<tr>
<td>Stereognosis</td>
<td>1,3-8,10,13-17</td>
<td>752 (16.9)</td>
<td>61 (36.0)</td>
</tr>
<tr>
<td>Graphesthesia</td>
<td>4-6,8-17</td>
<td>777 (27.8)</td>
<td>100 (18.1)</td>
</tr>
<tr>
<td><strong>Motor coordination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysdiadochokinesia</td>
<td>6,7,9,11-17</td>
<td>532 (13.5)</td>
<td>60 (1.7)</td>
</tr>
<tr>
<td>Tandem walk</td>
<td>6,9,11,15-17</td>
<td>484 (10.0)</td>
<td>60 (0.0)</td>
</tr>
<tr>
<td>Finger-thumb opposition</td>
<td>6,8,9,12,13,15-17</td>
<td>451 (20.6)</td>
<td>60 (0.0)</td>
</tr>
<tr>
<td>Finger-nose</td>
<td>6,8,10,14-17</td>
<td>541 (17.3)</td>
<td>-</td>
</tr>
<tr>
<td>Rhythm tapping</td>
<td>1,7,10-13,15-17</td>
<td>579 (41.8)</td>
<td>21 (75.8)</td>
</tr>
<tr>
<td><strong>Motor sequencing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fist edge palm</td>
<td>6,8,13,15,17</td>
<td>267 (46.0)</td>
<td>0 -</td>
</tr>
<tr>
<td>Oseretski</td>
<td>6,15-17</td>
<td>334 (37.2)</td>
<td>0 -</td>
</tr>
<tr>
<td>Fist ring</td>
<td>6,8,16,17</td>
<td>303 (27.7)</td>
<td>0 -</td>
</tr>
<tr>
<td><strong>Primitive reflexes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gaze</td>
<td>7,15-17</td>
<td>306 (21.7)</td>
<td>0 -</td>
</tr>
<tr>
<td>Palmomental</td>
<td>1,4,6-8,10,13,15,</td>
<td>458 (10.5)</td>
<td>39 (15.4)</td>
</tr>
<tr>
<td>Snout</td>
<td>6,7,10,15,17</td>
<td>460 (5.3)</td>
<td>-</td>
</tr>
<tr>
<td>Grasp</td>
<td>1,4,7,8,10,13,15,17</td>
<td>480 (8.0)</td>
<td>49 (14.3)</td>
</tr>
<tr>
<td>Suck</td>
<td>6,7,10,17</td>
<td>398 (4.5)</td>
<td>0 -</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk/limb dyskinesia</td>
<td>3,15</td>
<td>118 (27.5)</td>
<td>0 -</td>
</tr>
<tr>
<td>Tremor</td>
<td>6,15,17</td>
<td>236 (19.9)</td>
<td>0 -</td>
</tr>
<tr>
<td>Convergence</td>
<td>7,16,17</td>
<td>244 (26.4)</td>
<td>0 -</td>
</tr>
<tr>
<td>Articulation</td>
<td>1,3,9,11,12,14-16</td>
<td>289 (16.2)</td>
<td>81 (0.0)</td>
</tr>
<tr>
<td>Saccade</td>
<td>6,15</td>
<td>138 (12.9)</td>
<td>0 -</td>
</tr>
<tr>
<td>Imaginary acts</td>
<td>1,4,7</td>
<td>113 (60.0)</td>
<td>49 (50.2)</td>
</tr>
<tr>
<td>Romberg</td>
<td>6,8,15-17</td>
<td>365 (3.5)</td>
<td>0 -</td>
</tr>
<tr>
<td>Shuffling gait</td>
<td>8,15</td>
<td>93 (7.5)</td>
<td>0 -</td>
</tr>
<tr>
<td>Increased gait</td>
<td>9,12,15</td>
<td>148 (5.4)</td>
<td>60 (1.7)</td>
</tr>
<tr>
<td>Hopping</td>
<td>8,9,11,12,14,</td>
<td>181 (3.9)</td>
<td>60 (0.0)</td>
</tr>
<tr>
<td>Mirror movement</td>
<td>2,4,6,9,12,14-17</td>
<td>534 (24.1)</td>
<td>104 (34.6)</td>
</tr>
<tr>
<td>Face hand test</td>
<td>2,8,9,10-12,14</td>
<td>427 (10.7)</td>
<td>76 (8.4)</td>
</tr>
<tr>
<td>Extensor Plantar Response</td>
<td>6,8,9,15,</td>
<td>255 (4.2)</td>
<td>60 (0.0)</td>
</tr>
</tbody>
</table>
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. Bonferroni-Holm corrected P-values of chi-square tests between three diagnostic groups.

<table>
<thead>
<tr>
<th>Sensory integration</th>
<th>S/M</th>
<th>M/C</th>
<th>S/C</th>
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<tr>
<td>Extinction</td>
<td>0.03</td>
<td>NS</td>
<td>0.001</td>
</tr>
<tr>
<td>L-R disorientation</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Stereognosis</td>
<td>0.001</td>
<td>0.001</td>
<td>0.02</td>
</tr>
<tr>
<td>Graphesthesia</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<thead>
<tr>
<th>Motor coordination</th>
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<tr>
<td>Dysdiadochokinesia</td>
<td>0.02</td>
<td>NS</td>
<td>0.001</td>
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<tr>
<td>Tandem walk</td>
<td>0.02</td>
<td>NS</td>
<td>0.001</td>
</tr>
<tr>
<td>Finger-thumb opposition.</td>
<td>0.001</td>
<td>0.01</td>
<td>0.01</td>
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<td>-</td>
<td>-</td>
<td>0.01</td>
</tr>
<tr>
<td>Rhythm tapping</td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
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</table>

<table>
<thead>
<tr>
<th>Motor sequencing</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fist edge palm</td>
<td>-</td>
<td>-</td>
<td>0.001</td>
</tr>
<tr>
<td>Oseretski</td>
<td>-</td>
<td>-</td>
<td>0.001</td>
</tr>
<tr>
<td>Fist ring</td>
<td>-</td>
<td>-</td>
<td>0.001</td>
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</tbody>
</table>

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<tr>
<th>Primitive reflex</th>
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<tbody>
<tr>
<td>Gaze</td>
<td>-</td>
<td>-</td>
<td>0.001</td>
</tr>
<tr>
<td>Palmomental</td>
<td>NS</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Snout</td>
<td>-</td>
<td>-</td>
<td>0.01</td>
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<tr>
<td>Grasp</td>
<td>NS</td>
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<th>Other</th>
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<tr>
<td>Trunk/limb dyskinesia</td>
<td>-</td>
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<td>0.001</td>
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<td>Tremor</td>
<td>-</td>
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<tr>
<td>Convergence</td>
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<td>Articulation</td>
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<td>Saccade</td>
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<td>0.001</td>
</tr>
<tr>
<td>Imaginary acts</td>
<td>NS</td>
<td>NS</td>
<td>0.001</td>
</tr>
<tr>
<td>Romberg</td>
<td>-</td>
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<td>Shuffling gait</td>
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<td>Increased gait</td>
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<td>NS</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Mirror movement</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>face hand test</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Extensor Plantar response</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

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
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 overweighed. Although there is consistency in the assessment procedures, the possibility of assessment bias cannot 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.
REFERENCES


Bender, M.D., Fink, M., Green, M., 1951. Patterns in perception on simultaneous tests of face and hand. Arch Neurol Psychiatry. 66, 355-362.


Review


Paulson, G.W., 1971. The neurological examination in dementia. C.E.Wells (Ed.), Dementia. F.A. Davis,
Chapter 5

Philadelphia.


CHAPTER 6

NEUROLOGICAL SOFT SIGNS
DISCRIMINATING MOOD DISORDERS FROM FIRST EPISODE SCHIZOPHRENIA.

Marco P.M. Boks, Peter F. Liddle, Johannes G.M. Burgerhof, Rikus Knegtering, Robert J. van den Bosch.
ABSTRACT

Objective: To investigate the specificity of neurological soft signs (NSS) for first episode schizophrenia compared to mood disorders. Method: We assessed NSS in a sample of 60 healthy controls, 191 first episode psychosis patients and 81 mood disorder patients. We used a principle component analysis to identify dimensions of NSS. We subsequently investigated the specificity of these dimensions for schizophrenia and their relationships with medication and symptom scores. Results: We identified 5 dimensions; coordination disorders, movement disorders, increased reflexes, dyskinesia and catatonia. These dimensions were related to neural circuits associated with schizophrenia and mood disorders and included the fronto-striatal-thalamic and the fronto-cerebellar pathway. The movement disorder dimension, which was suggestive for the involvement of the fronto-striatal-thalamic pathway, was specific for first episode schizophrenia independent from medication. Conclusion: NSS are the result of circuitry dysfunctions rather than overall dysfunction and a particular set of NSS shows specificity for schizophrenia.

INTRODUCTION

In the past years our knowledge about NSS in first episode psychosis has rapidly increased. It has become clear that the prevalence of NSS is higher in first episode psychosis compared to healthy volunteers and is also present in medication naive schizophrenia patients (Venkatasubramanian et al. 2003). However NSS are also apparent in numerous other psychiatric disorders including mood disorders (Boks et al. 2000). Therefore further research is required to investigate the specificity of NSS for schizophrenia (Dazzan and Murray 2002). Particularly because the presence of NSS in other psychiatric disorders does not rule out the possible existence of NSS, or indeed categories of NSS, that are specific to schizophrenia. In our review (Boks et al. 2000) we found evidence of increased NSS in schizophrenia and mood disorders but could not find evidence for a clearly interpretable pattern. Therefore we hypothesised that the current categories or clusters of NSS were relatively uninformative about the diagnostic significance of NSS. Although over the past decades several categories of NSS have been composed (Kinney et al. 1991; Chen et al. 1995; Buchanan and Heinrichs 1989; Kinney et al. 1999; Matsumoto et al. 2001) none of them was based on an empirical method. Only the division of signs by Kinney et al. (1999) was suggestive for possible aetiology of NSS. Therefore the neuropathology of NSS remains subject to debate.

From all assessments the Neurological Evaluation Scale (NES) was most frequently used and also the only scale with validated categories of NSS in terms of internal consistency (Buchanan and Heinrichs 1989). However the NES is not fully comprehensive and the categories are not based on an empirical method. The Cambridge Neurological Inventory (CNI) (Chen et al. 1995) is the most comprehensive assessment, but in term does not present validated categories nor measures of internal consistency. With this study we attempt to illuminate the complex relationship between diagnosis and NSS. This could improve our insight in possible underlying neuropathology.
Aim of the study is to identify meaningful empirical categories of NSS, which show internal consistency. Subsequently we examine the differences between first episode schizophrenia and mood disorder patients, controlling for age and medication effects, in order to establish which NSS are specific for schizophrenia. Finally, we investigate the relationships between these newly derived dimensions of NSS and symptom profile in the first episode schizophrenia group.

METHODS

From 1996 to 2002 all newly admitted patients, aged between 18 and 55, in the department of psychiatry at the university hospital Groningen with a first episode psychosis and all patients admitted with a clinical depression between 1999 and 2001 were asked to participate in this study. After complete description of the study written informed consent was obtained. The subjects were investigated by means of the CNI (Chen et al. 1995), a comprehensive standardised neurological investigation. This inventory includes 76 NSS and includes most NSS from the NES (Buchanan and Heinrichs 1989) along with other NSS. Three trainees in psychiatry and one neurologist conducted the examinations. Interrater reliability between raters for the total score was assessed in 40 subjects and was good (intraclass correlation = 0.83). Raters were blind to the hypothesis but not to the diagnosis. Diagnosis were made according DSM IV by means of the SCAN interview (Wing et al. 1990). Healthy volunteers were recruited with several advertisements in local papers. They received a semi-structured interview to assess medical history and current complaints. Only volunteers without personal psychiatric history, with a negative psychiatric family history and without current medication were included. Subjects with a score higher than 2 on the General Health Questionnaire (Goldberg and Williams 1988) were also excluded to avoid morbidity in the volunteers.

We analysed our data in three steps. Firstly we reduced the number of signs for inclusion in the subsequent analysis by excluding those signs which did not discriminate between patients and controls. Secondly we identified the categories of NSS in the pooled patients by using a principal component analysis. Finally we investigated whether the derived dimensions showed specificity for the schizophrenia group independent from possible confounders and how these dimension related to symptoms. In the schizophrenia group we included patients with schizophrenia and schizophreniform disorder.

Because the ratio of variables from the CNI compared to the number of cases was high, we reduced the number of signs first. After we established the absence of significant right/left differences we took the means of the signs where both sides were rated. Furthermore, because we were only interested in those signs that distinguished between patients and normal controls, we only included NSS from our dataset that showed a significant difference between both groups (Mann-Whitney tests with a significance level of 0.05). We did not correct for multiple comparisons because the tests were only intended for the reduction of number of signs. With the resulting subset of 50 signs we conducted a principal component analysis with subsequent Varimax rotation with Kaiser normalisation. We designated a factor loading of 0.45 as acceptable. We based the number of factors on a scree plot and we calculated the Cronbach’s \( \alpha \) as a measure of internal consistency.
Subsequently we investigated the specificity of the NSS dimensions for the diagnostic groups. However, we needed to correct for the possible influence of confounding variables such as medication, age and sex, on the dimension scores. We therefore used binary logistic regression with as the predicted variable diagnosis (either schizophrenia or mood disorder) and as the predictor variables the NSS dimension scores, medication variables, age and sex. We did not use multivariate analysis of variance because the variance in the data was not homogeneous. We entered (conditional forward) into our model; the factor scores, age and five binary variables representing the presence or absence of antidepressants, mood stabilizers, classical antipsychotics, atypical antipsychotics and male sex. We designated as atypical antipsychotics; olanzapine, risperidone, quetiapine, ziprasidone, amisulpiride, sertindole and clozapine. We had PANSS (Cantor-Graae et al. 1997) data available for 93 of the 128 patients of the first episode schizophrenia group and in 142 of the 191 first episode psychosis patients. This limited availability was the result of logistic problems in obtaining PANSS data for all first episode psychosis patients and not the result of selection. To investigate the relationships between PANSS score and factor scores we chose the following approach. Because the factor scores were not normal distributed, we categorized the scores in quintiles. We subsequently used nominal regression to estimate the influence of the PANSS scores on the factor scores. In the model we included the five factor division of the PANSS (Gunduz et al. 1999), the dosage of antipsychotics in haloperidol equivalents based on D2 occupancy (Schotte et al. 1996), and the presence or absence of antidepressant drugs.

**RESULTS**

332 subjects were included in this study: 60 healthy control subjects, 191 patients with a first episode psychosis (41 patients with schizophreniform disorder, 87 schizophrenia, 26 schizoaffective disorder, 17 brief psychosis, 7 delusional disorder, 13 psychosis NOS) and 81 patients with a clinical depression (40 patients with unipolar depressive disorder, 30 patients with depressive phase of a bipolar mood disorder, 5 patients with mood disorder NOS and 6 patients with depressive episode with psychosis). Table 1 shows the clinical and demographic data of the pooled patient group (used to extract the factor structure), the schizophrenia group and the mood disorder group.

**Table 1: Demographic variables.**

<table>
<thead>
<tr>
<th></th>
<th>Pooled Patients</th>
<th>Schizophrenia group</th>
<th>Mood disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>272</td>
<td>128</td>
<td>81</td>
</tr>
<tr>
<td>Mean age (S.D.)</td>
<td>28.9 (8.5)</td>
<td>26.2 (6.0)</td>
<td>33.7 (10.8)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>177 (65%)</td>
<td>94 (73%)</td>
<td>44 (54%)</td>
</tr>
<tr>
<td>Antipsychotics (%)</td>
<td>199 (73%)</td>
<td>112 (88%)</td>
<td>42 (52%)</td>
</tr>
<tr>
<td>Mean dose (S.D.)</td>
<td>4.3 (4.1)</td>
<td>5.5 (4.4)</td>
<td>2.8 (3.9)</td>
</tr>
<tr>
<td>Antidepressants (%)</td>
<td>56 (21%)</td>
<td>7 (5.4%)</td>
<td>40 (49.4%)</td>
</tr>
<tr>
<td>Mood stabilisers (%)</td>
<td>14 (0.5%)</td>
<td>0 (0.0%)</td>
<td>10 (12.0%)</td>
</tr>
</tbody>
</table>
Based on a scree-plot (figure 1) we chose to extract five components. The derived factors are presented in table 2 with factor loadings and Cronbach's alpha. Five factors accounted for 30.4% of the shared variance. The Cronbach's alpha was satisfactory, ranging from 0.58 to 0.77.
### Table 2: Factors with loadings, explained variance and intra class correlation.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Signs</th>
<th>loading</th>
<th>Explained Variance (%)</th>
<th>Cronbach’s α</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 coordinatio - dis orders</td>
<td>Tandem walk</td>
<td>0.76</td>
<td>12.0</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Finger-thumb tapping</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Finger thumb opposition</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Balance</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Finger-nose test</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor articulation</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unintelligible speech</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysdiadochakinesia</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 movement disorders</td>
<td>Saccade smoothness</td>
<td>0.59</td>
<td>5.1</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>Smoothness SPEM</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postural tremor</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mirror movement</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gait decreased movements</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resting tremor</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Saccade blink suppression</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impersistent tongue protrusion</td>
<td>0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased reflexes lower limbs</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Increased reflexes</td>
<td>Increased reflexes lower limb</td>
<td>0.66</td>
<td>5.2</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>Increased reflexes upper limb</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Dyskinesia</td>
<td>Complex/Stereotype Head Movement</td>
<td>0.75</td>
<td>4.5</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Trunk-limb mannerism</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Facial dyskinesia</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trunk-limb dyskinesia</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Catatonia</td>
<td>Mitgehen</td>
<td>0.58</td>
<td>3.6</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>Increased tone arms</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased tone lower limbs</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased reflexes</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Underactivity</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 2: Mean score and 95% Confidence Interval (CI) on the factors per diagnostic group.

Figure 2 shows the mean scores and 95% confidence intervals on the factors per diagnostic group demonstrating the differences in the scores on particularly factor 2. However the schizophrenia group was significantly younger (t-test two tailed, t= 5.7, p<0.001) and included more male patients (chi square = 8.1, p=0.004). And as can be expected used antipsychotics more frequently (chi square = 33.1, p<0.001) and in higher doses (t-test two tailed, t= 4.7, p<0.001) in contrast to the mood disorder group. The latter used antidepressants (chi square = 54.9, p<0.001) and mood stabilisers (Fisher Exact, p<0.001) more frequently.

Table 3: Variables in the binary regression model predicting diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moodstabilizers</td>
<td>11.96</td>
<td>.848</td>
<td>22,546</td>
<td>1</td>
<td>.000</td>
<td>45,249</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>3.267</td>
<td>.455</td>
<td>31,443</td>
<td>1</td>
<td>.000</td>
<td>13,920</td>
</tr>
<tr>
<td>Age</td>
<td>0.110</td>
<td>.027</td>
<td>16,221</td>
<td>1</td>
<td>.001</td>
<td>1,114</td>
</tr>
<tr>
<td>Classical antipsych.</td>
<td>-1.157</td>
<td>.508</td>
<td>3,754</td>
<td>1</td>
<td>.019</td>
<td>0,303</td>
</tr>
<tr>
<td>Atypical antipsych.</td>
<td>-1.718</td>
<td>.507</td>
<td>8,252</td>
<td>1</td>
<td>.002</td>
<td>0,209</td>
</tr>
<tr>
<td>Factor2</td>
<td>.4836</td>
<td>.195</td>
<td>6,140</td>
<td>1</td>
<td>.013</td>
<td>0,130</td>
</tr>
<tr>
<td>Constant</td>
<td>-3,058</td>
<td>1.15</td>
<td>12,610</td>
<td>1</td>
<td>.008</td>
<td>0,031</td>
</tr>
</tbody>
</table>
Chapter 6

Table 3 shows the statistics of our binary logistic regression model. As expected, the usage of antidepressants, mood stabilisers and antipsychotics was related to the diagnosis. And in agreement with the fact that patients in the first episode schizophrenia group were significantly younger compared to the mood disorder patients, age was also a good predictor of diagnosis in our sample. Factor 2 (movement disorders) was significantly higher in the schizophrenia group ($\beta=0.48$, $p=0.013$) independent from medication and other confounders. The overall fit of the models was satisfactory (Nagelkerke R-square = 0.67).

We further investigated the neurological soft sign dimensions by exploring the relation between factor scores and possible confounding variables. There was a significant greater male-to-female ratio in the first episode schizophrenia group compared to the mood disorder group but no significant differences on factor scores between the male and female patients. There also was no correlation between age and any of our dimensions of NSS.

There was a significant but small positive correlation between the movement disorder dimension and the dose of antipsychotics haloperidol equivalents based on D2 occupancy (Kendall’s tau; 0.16, $p<0.001$). When focussing on the first episode schizophrenia group alone, the correlation was similar (Kendall’s tau; 0.20 $p<0.01$). In mood disorder patients this correlation was absent (Kendall’s tau; 0.04 $p=0.68$). After correction for multiple comparisons, patients on antipsychotics scored significantly higher on the movement disorder dimension compared to patients without antipsychotics (Mann-Whitney $Z=2.8$ $p=0.006$). However this could be the result of the fact that in first episode schizophrenia group, patients were two times more likely to use antipsychotics and had significantly higher doses of antipsychotics. To further explore the influence of antipsychotics, we compared the dimension scores between patients on classical and on atypical antipsychotics. We found that scores on the movement disorder dimension was significantly higher in patients on classical compared to patients on atypical antipsychotics (Mann-Whitney $Z=4.0$, $p<0.001$). This difference remained significant within the schizophrenia group alone. Moreover this relationship was independent from the extra-pyramidal signs included in this factor; tremor in rest and decreased movements in gait. There were no differences in the ratios of patients on typical versus atypical antipsychotics, between the first episode psychosis and mood disorder groups.

No differences on dimension scores could be found between the groups of patients with and without antidepressant treatment.

We explored the relationship between symptom profile and the NSS in the patients with first episode psychosis group and the subgroup of first episode schizophrenia by means of nominal logistic regression. From the model we found that factors 3 (increased reflexes), 4 (Dyskinesia) and 5 (Catatonia) were associated with negative symptoms ($\text{Chi-square }= 7.1$, $p=0.03$, $\text{Chi-square }=11.9$, $p=0.02$, $\text{Chi-square }=11.3$, $p=0.02$); factor 5 was also associated with depressive symptoms ($\text{Chi-square }=11.3$, $p=0.02$) and factors 1 (coordination) and 2 (movement) were independent of the symptom profile. In the schizophrenia group only, the factors were independent from symptom profile.
DISCUSSION

This is the first study to identify a set of NSS that discriminates first episode schizophrenia and schizophreniform disorder patients from mood disorder patients independent from medication and other possible confounders. It presents five categories of NSS that are suggestive of specific underlying neuropathology. They seem to point to the involvement of several specific pathways in NSS rather than the involvement of single brain structures or overall dysfunction.

The first dimension mainly consists of coordination tasks and seems to reflect fronto-cerebellar malfunctions. It consists of the traditional cerebellar tasks of tandem walk, dysdiadochokinesia and balance, and fronto cerebellar coordination tasks such as finger nose and finger tapping combined with articulation, speech and tongue movement (Leiner et al. 1986). The latter signs are to a large extent dependent on frontal brain regions and it is interesting to note that cognitive tests such as the verbal fluency test, which is impaired in schizophrenia patients (Heinrichs and Zakzanis 1998), combines speech functions with frontal cognitive impairment. Recent studies have also pointed to the role of the cerebellum in cognitive functions (Rapoport et al. 2000) and cerebellar dysfunction has already been related to schizophrenia (Eluri et al. 1998; Katsetos et al. 1997) and depression (Sweeney et al. 1998). Furthermore the theory of “cognitive dysmetria” (Andreasen et al. 1999; Nopoulos et al. 1999) associates cognitive dysfunction and impaired motor coordination with cerebellar dysfunction. Our results therefore seem to support evidence for the involvement of the cerebellum in schizophrenia and mood disorders. They also suggest a common pathway of both coordination and speech difficulties. This is therefore suggestive of the involvement of the dorsolateral prefrontal cortex in this particular dimension.

The second dimension is largely composed of items usually regarded as parkinsonian, and eye movement disorders. The combination of eye movement disorders with other motor dysfunctions is supported by evidence of the relationship between motor tasks and eye movement disorders (Schlenker et al. 1994; Ross et al. 1998). In eye movement disorders frontal cortical structures such as the frontal eye-field are involved along with regions within the midbrain and brainstem. In impersistent tongue protrusion, mirror movements and saccade blink suppression; the common denominator, lack of inhibition, points to the involvement of the frontal cortex. The inclusion of tremors, decreased reflexes of the legs and decreased movements in gait seem to be pointing to the involvement of the basal ganglia in this dimension. The inclusion of reduced reflexes of the lower limbs in this dimension is surprising. However, it has a factor loading just above our threshold. It is therefore not unlikely that the inclusion of this particular sign is an artefact. Overall, all of the included signs in this dimension seem dependent on the fronto-striatal-thalamic pathway. Indeed, the involvement of the basal ganglia would explain the small but significant correlation with the use of antipsychotics. In that respect it is interesting to note that this dimension is the only dimension that is influenced by antipsychotics which concurs with evidence of the importance of the mesolimbic dopaminergic circuit as a target area of antipsychotic treatment (Joyce et al. 1997).

The inclusion of eye movement disorders in the most specific dimension is consistent with the growing evidence of the specificity of eye movement disorders for schizophrenia (Mahlberg et
Gschwandtner et al. (2001) suggested the use of a combination of eye-movement and fine motor functioning assessment as a marker for the early detection of psychosis. The influence of antipsychotics on eye movement disorder is subject to debate. There is evidence of the absence of influence of conventional antipsychotics in the short term, but increased influence in the long term (Levy et al. 1993; Crawford et al. 1995; Hutton et al. 2001). As the subjects in our study were first episode schizophrenia and schizophreniform disorder patients their exposure to antipsychotics was short and the influence of classical antipsychotics on their eye-movements therefore limited. In accordance with the relationship we found between this dimension and the use of atypical antipsychotics, there is compelling evidence that atypical antipsychotics do improve eye movement disorders even in the short term (Sweeney et al. 1997; Friedman et al. 1992).

Dimension 3 (increased reflexes) has the fewest items and consists only of increased reflexes. The observed relationship with the negative symptom score on the PANSS after controlling for diagnosis and medication remains to be explained. Dimension 4 clearly consists of dyskinesia signs. It is interesting to note that this dimension does not distinguish mood disorder patients from first episode patients but does discriminate between control subjects and patients. This is consistent with previous evidence that dyskinesia occurs in both schizophrenia and mood disorders (Van Os et al. 1997). In agreement with earlier reports on the relationship between tardive dyskinesia and negative symptoms (Gattaz et al. 1992) the dyskinesia dimension is related to the negative dimension on the PANSS score.

The common denominator of dimension 5 lies in the association with catatonia signs. Decreased reflexes, underactivity and ‘mitgehen’ (related to waxy flexibility) are core features of the classical concept of catatonia. Increased muscular tone seems to contradict with decreased reflexes but would cluster together as different presentations of catatonia, with and without increased motor activity (Joseph 1999). It concurs with evidence that catatonia signs are more apparent in schizophrenia compared to healthy controls, but are not discriminating mood disorders from schizophrenia (Starkstein et al. 1996). Moreover the relationship between scores on the negative dimension of the 5 factor PANSS division and factor 5 is similar to the relationship between catatonia and negative symptoms (Chen et al. 1996; Dhossche and Petrides 1997). The relationship between the depression dimension of the PANSS and factor 5 (Catatonia) remains unexplained as yet. However we hypothesise it might be the result of motivational problems in first episode schizophrenia group with depressed features during the assessment of these signs.

It must be pointed out that the assessment of the eye-movement disorders was based on observation only and no electrophysiological measures were taken. Therefore caution with the interpretation of the meaning of the movement disorder dimension is appropriate. Neuro-imaging or other brains mapping studies are required to confirm our findings. The fact that the mood disorder group in contrast to the schizophrenia group was not a first episode group might account for some differences between the groups but we consider it is unlikely to account for our main findings. There is evidence that NSS are not related to age or illness duration (Chen et al. 2000). Moreover, if there was a systematic effect one would expect an increase in NSS with age and illness duration in the mood disorder group which would obscure the differences between groups. Whereas it is increasingly clear that cognitive function
is an inherent part of psychiatric disorders it would be informative to see how our dimensions relate to cognitive functions. Especially since both the cortico-cerebellar and cortico-striatal-thalamic pathways are associated with cognitive dysfunction.

Overall this study suggest that NSS are the representation of well knows concepts within schizophrenia and mood disorders. As we found the differences between schizophrenia and mood disorders for most NSS to be gradual, this study concurs with an increasing number of studies pointing towards a continuity of schizophrenia and affective disorders from a clinical and genetic perspective (Maier et al. 1993; Taylor 1992; Wildenauer et al. 1999).

Nevertheless we did find clear differences between the two diagnostic groups. The movement disorder dimension of NSS discriminates mood disorder and schizophrenia group independent of medication. Our study therefore supports the hypothesis that the impairment in the cortico-striatal-thalamic circuit is one of the most specific findings in schizophrenia (Weinberger et al. 1992). The influence of atypical antipsychotics on the movement disorder dimension is noteworthy. Our data points to an influence of atypical antipsychotics on this dimension of NSS and therefore to an influence of atypical antipsychotics on the fronto-striatal-thalamic pathway. Because this influence does not manifest itself in changes in the extra-pyramidal signs it is suggestive of an influence of atypical antipsychotics on the fronto-striatal-thalamic pathway as a whole rather than on the striatum alone. Although this is not a new finding, it is a confirmation of the validity of our approach. As was the discovery of additional evidence of the influence of the cerebellum in schizophrenia and mood disorders.
Chapter 6

REFERENCES


Factor analysis


Chapter 6

Psychiatry. 149, 22-32.
Wing, J.K., Babor, T., Brugha, T., Burke, J., Cooper, J.E., Giel, R., Jablenski, A., Regier, D., Sartorius, N., 1990. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry. 47, 589-593.
NEGATIVE ASSOCIATION BETWEEN A HISTORY OF OBSTETRIC COMPLICATIONS AND THE NUMBER OF NEUROLOGICAL SOFT SIGNS IN FIRST-EPIODE SCHIZOPHRENIC DISORDER.

Marco P.M. Boks, Jean-Paul Selten, Stuart Leask, Stynke Castelein, Robert J. van den Bosch.
SUMMARY

We examined the relationship between having a history of obstetric complications (OCs) and the number of neurological soft signs (NSS) in a group of 132 patients experiencing their first episode of psychosis. Contrary to our expectations we found a negative relationship between these two measures. It is possible that the patients with a history of OCs carry fewer susceptibility genes for schizophrenia and NSS than those without a history of OCs.

INTRODUCTION

There is compelling evidence of an increased number of NSS in first episode psychosis (Dazzan and Murray, 2002) and schizophrenia (Boks et al., 2000; Leask et al., 2002). Furthermore, some see OCs as risk factors for schizophrenia (see Cannon et al., 2002, although see also Crow, 2003). The observation that both NSS and OCs are associated with an increased ventricle to brain ratio (Wright et al., 2000; Owen et al., 1988) leads to the hypothesis that OCs might contribute to the development of NSS. Consequently, we tested the hypothesis that the presence of a history of OCs is related to a greater number of NSS in schizophrenia.

METHOD

We examined 132 consecutive first admissions for a first episode psychosis, including 92 patients with a diagnosis of a ‘schizophrenic disorder’ (DSM-IV: 295.x: schizophrenia, schizophreniform or schizoaffective disorder). The patients had been diagnosed with; schizophrenia (N=47), schizoaffective disorder (N=20), schizophreniform disorder (N=25), drug induced psychotic disorder (N=10), brief psychotic disorder (N=10), psychotic disorder not otherwise specified (N=7), mood disorder with psychotic features (N=9), delusional disorder (N=4). Eighty-three patients (63%) were male, the mean age was 25.9 years (SD 5.8). Thirty-two patients were not on antipsychotics. The other patients used; olanzapine (N=32), risperidone (N=31), pimozide (N=10), quetiapine (N=8), haloperidol (N=5), zuclopenthixol (N=5), sertindole (N=3), clozapine (N=2), perphenazine (N=2), penfluridol (N=1). The mean dosage in haloperidol equivalents was 4.1 mg (SD 3.4). Ten patients (8%) were left-handed, in 5 patients (4%) handedness was mixed. Seventeen patients (13%) had a history of head trauma.

After complete description of the study written informed consent was obtained. DSM IV diagnoses were established by means of the SCAN interview (Wing et al., 1990). Information on handedness and history of head trauma was assessed by a semi-structured interview. Six weeks after admission all patients underwent a standardized comprehensive neurological investigation, the Cambridge Neurological Investigation (Chen et al., 1995). Interrater reliability between three raters had been assessed in a random sample of 30 cases and was satisfactory (ICC 0.83). Previously we reported on significant increase in the number of NSS in patients versus healthy controls (Boks et al., 2004).
The biological mother completed a questionnaire on several pregnancy, labor-delivery and neonatal complications. We focused on the 10 OCs that had been shown to be significant risk factors for schizophrenia in the Cannon et al. meta-analysis (2002): diabetes in pregnancy, birth weight <2000 g and birth weight <2500 g separately, emergency caesarian section, congenital malformations, uterine atony, rhesus antagonism, asphyxia, bleeding in pregnancy, and preeclampsia.

We tested differences in the number of NSS between groups with or without OCs using an independent, two-tailed t-test. The analyses were conducted for the entire group, and for the schizophrenic disorder group and the other psychotic disorder group separately.

Table 1: Characteristics of the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenic disorders</th>
<th>Other psychotic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No OC</td>
<td>OC</td>
</tr>
<tr>
<td>N</td>
<td>62</td>
<td>30</td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>26.1 (5.6)</td>
<td>26.2 (6.9)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>42 (68%)</td>
<td>20 (68%)</td>
</tr>
<tr>
<td>Not right handed (%)</td>
<td>5 (8.1%)</td>
<td>4 (13.3%)</td>
</tr>
<tr>
<td>Head trauma (%)</td>
<td>6 (9.7%)</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>Dosage haloper. Eq (SD)</td>
<td>5.4 (3.5)</td>
<td>4.2 (2.3)</td>
</tr>
<tr>
<td>Total score NSS (SD)</td>
<td>10.3 (6.9)</td>
<td>7.3 (5.9)</td>
</tr>
<tr>
<td>High NSS (%)</td>
<td>35 (56%)</td>
<td>12 (40%)</td>
</tr>
</tbody>
</table>

RESULTS

Table 1 shows the characteristics of patients with a schizophrenic disorder and those with other psychotic disorders, divided into patients with and without OCs. There were no significant differences in age, sex and dosage of antipsychotics, history of head trauma or handedness between any of the subgroups.

Contrary to our hypothesis we found a significantly smaller number of NSS in the total group of patients with a history of OCs; 7.0 vs. 9.6 respectively (t=2.0 df=130 p=0.049). The same was found in the subgroup of schizophrenic disorder patients with a history of OCs (t=2.07 df=90 p=0.04). In the group of patients with other psychotic disorders the differences were not significant (t=0.704 df=37 p=0.48). To exclude the possibility that the differences in the dosage of antipsychotics accounted for the differences between patients with and without history of OCs we tested the differences between these groups with the dosage as a covariate. For the entire group the differences no longer reached significance (F= 2.56 df=2 p=0.08). However in the schizophrenic disorder group the differences were amplified (F= 3.63 df=2 p=0.03).
Chapter 7

**DISCUSSION**

This study finds a significant but negative relationship between the number of NSS and a history of OCs in first episode patients with a schizophrenic disorder. Strength of this study is its use of standardized neurological and diagnostic assessments. A limitation of this study is the use of maternal information on OCs. However, this is likely to lead to an overestimation of OCs in patients compared to healthy control subjects (Buka et al., 2000) and in our study we did not include controls.

To our knowledge there have been only 2 studies that addressed this topic. One was negative (Cantor-Graae et al., 1994). Another found a positive relationship between NSS and OCs in male schizophrenia patients, but not in female patients (Lane et al., 1996).

How to explain a negative association between a history of OCs and the number of NSS? Several studies have found that the number of NSS is strongly associated with a positive family history of schizophrenia (Ismail et al., 1998; Cantor-Graae et al., 2000). Consequently, it is possible that the patients with a history of OCs carry fewer genes for schizophrenia (and NSS), and ‘needed’ the further neurodevelopmental insult of OCs to develop schizophrenia.
ACKNOWLEDGEMENT

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REFERENCES


Wing, J.K., Babor, T., Brugha, T., Burke, J., Cooper, J.E., Giel, R., Jablenski, A., Regier, D., Sartorius, N., 1990. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry. 47, 589-593.

CHAPTER 8
DISCUSSION AND CONCLUSION
Despite extensive research in the past decades our knowledge on neurological soft signs (NSS) has only showed limited progress and the exact meaning of NSS has remained obscured. Two domains of explanations for this limited progress can be distinguished. Firstly the methodological issues such as measurability and reliability. Secondly issues relating to the often complex relationships between NSS and a broad variety of confounding variables such as IQ, age, diagnosis, handedness, premorbid functioning, obstetric complications, tardive dyskinesia, catatonia and so on. In our introduction we discussed the potential suitability of NSS as an endophenotype for schizophrenia based on criteria of measurability, reliability and specificity.

MEASURABILITY

As pointed out in the introduction, the assessments of NSS have vastly improved over time with the introduction of standardised assessments. In the past decade numerous tools have been developed for the assessment of NSS. However to date there is no consensus on exactly which signs should be incorporated in NSS assessments. Among others there is debate on the inclusion of EPS and TD signs and on the inclusion of primitive reflexes and eye movement disorders. Assessments also vary regarding the sequencing and motor coordination tests. As a consequence the number of signs varies between assessments and particularly motor coordination signs (Manschreck et al. 1985; Walker 1981) and sensory signs (Kinney et al. 1999; Martin et al. 1995) have been the focus of separate studies. To date the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs 1989) is the most frequently used but has substantial overlap with the Cambridge Neurological Investigation (CNI) (Chen et al. 1995) which is the most comprehensive. The use of the CNI in our studies did allow us to study the broadest variety of signs, the trade off being that our data was not comparable with the majority of studies. A more obscured issue regarding measuring NSS is that of the type of outcome variable. The NES and the CNI and most other assessments measure NSS on an ordinal scale (ie. absent, unclear, present, marked). This process of rating is subject to measurement bias (chapter 2). The scores are subsequently transformed to either total scores or scores on categories of signs. To avoid multiple comparison-issues generally the sum-scores are used for statistical testing. However the compositions of these categories are debatable. In our literature review we could not find a clear pattern of NSS based on the specificity of NSS for schizophrenia (chapter 5). However the categories of NSS we derived by means of a principle component analysis of those signs distinguishing patients from controls, revealed a pattern of NSS that was related to established abnormalities in schizophrenia but deviated from traditional categories of NSS (chapter 6). The lack of clarity regarding the inclusion of NSS in the assessments therefore adversely affects the measurability.

Because the majority of subjects under study will have only a limited number of NSS the scores on the majority of signs will be zero. As a consequence the distribution of the outcome measures of NSS assessments will be seriously skewed and depart from normality and have a substantial measurement error. As an endophenotype this provides a serious disadvantage compared to alternative endophenotypes such as fMRI abnormalities. In this respect it is interesting to note a promising new development in the rediscovery of some early assessment tools for movement disorders as a means to assess NSS such as a computerised pin board (Henkel et al. 2004).
RELIABILITY

Reliability can be broadly divided in test-retest reliability and inter-raters reliability. We measured NSS simultaneously by two raters and calculated measures of consistency between raters, which ranged from poor to good for the categorical scores and was good for the overall score (chapter 2). Establishing the test retest reliability of NSS is considerably more complicated and is related to issues of temporal stability of NSS and the relationships of NSS with symptoms, medication and other confounding variables. If NSS are to provide an endophenotype for schizophrenia the NSS should represent a stable trait independent from changeable confounders such as medication, movement disorders and symptoms. However in contrast to the required independence of NSS from medication some studies did find effects of prolonged medication exposure on NSS (King et al. 1991; Gupta et al. 1995). This is likely to be the result of the fact that extra-pyramidal signs and tardive dyskinesia signs are influenced by medication and consequently NSS are subject to change in those NSS assessment scales that include EPS and TD signs. It also seems plausible that NSS that are related to EPS and TD signs such as motor-sequencing tasks show a relationship with medication as indeed was found by Egan et al. (Egan et al. 2001). In contrast, the majority of studies into the effect of medication on NSS have argued against such a relationship (Ismail et al. 1998; Heinrichs and Buchanan 1988) and increased NSS have also been reported in medication naïve schizophrenia patients (Venkatasubramanian et al. 2003). We studied the relationship between antipsychotic medication and NSS by means of a cross sectional study were we compare the influence of atypical and classical antipsychotic drugs on NSS, TD and EPS in a group of first episode psychosis patients (chapter 4). We found that the number of NSS was not influenced by the type of medication insofar they did not incorporate TD signs. However the type of medication did influence the number of TD signs. It is therefore likely that NSS are independent from medication insofar the assessments do not incorporate EPS and dyskinesia signs.

The relationship between symptom profile and NSS has been investigated extensively with contradicting results. Studies presenting an association between NSS and symptom severity or profile (Tucker et al. 1975; Manschreck et al. 1981; Manschreck et al. 1981; Braun et al. 1995; Manschreck et al. 1981; Manschreck and Ames 1984; Wong et al. 1997; Browne et al. 2000; Flashman et al. 1996) are balanced by studies refuting this (Flyckt et al. 1999b; Kolakowska et al. 1985; Sanders et al. 1994; Merriam et al. 1990). We explored the relationship between symptom profile and NSS in patients with first episode schizophrenia and found the NSS to be independent from symptom profile (see chapter 6). Overall it is noteworthy that the relationship between movement disorders and negative symptoms is much better documented (Pantelis et al. 2001; Van Os et al. 1997) and that in this respect NSS differ from movement disorders.

Age is another potential confounder and changeable by definition. A relationship with NSS is suggested by studies presenting increased numbers of NSS in elderly patients (Jenkyn et al. 1985). Until recently few longitudinal studies have been published (Smith et al. 1999; Torrey 1980; Chen et al. 2000) predominantly in patients with chronic schizophrenia. However very recently, 2 studies have been published (Chen et al. 2005; Emsley et al. 2005) likely the result of increased interest in NSS as an endophenotype for the vulnerability to schizophrenia. We found no significant changes in the numbers of NSS 2-years after a first episode of psychosis.
However, the number of NSS was increased in patients with an increase of medication. These findings concur with the majority of the evidence suggesting that NSS do show temporal stability, but subsets of NSS may show variation related to symptom profile and clinical outcome.

In the introduction we already discussed the theoretical relationship between movement disorders and NSS. Whereas the relationship with medication is thoroughly investigated, the relationship with movement disorders is not. Direct comparison of patients with TD and those without revealed no significant differences with regard to the presence of neurological “soft” signs (Gureje 1987) (chapter 4). In contrast, primitive reflexes, a category sometimes included in NSS have been found to be related to TD (Youssef and Waddington 1988). The scarcity of studies into the relationship between NSS and movement disorders and the similarities between them emphasizes the need for further study into the question whether EPS and TD are the result of a similar neurodevelopmental vulnerability as NSS and to what extent there is overlap and separation of the underlying processes.

Although with the above the most apparent confounders are discussed the list of potential confounders is longer and the discussion beyond the scope of this thesis. Other potential confounders include among others; alcohol and substance abuse (Douyon et al. 1998;Keenan et al. 1997), cognitive function, premorbid adjustment, aggression, acathesia, family loading for schizophrenia, neuroticism, negative symptoms, aggression, disorganisation.

SPECIFICITY

Numerous studies have found NSS in a vast variety of psychiatric disorders apart from schizophrenia and mood disorders. NSS have been reported in alcoholism, PTSD, senescence, bipolar disorder, trichotillomania, violent adolescents and so on. Similar to the poor specificity of the majority of findings in schizophrenia such as neuropsychological measures, this does not rule out a pattern of symptoms in which NSS or categories of NSS may be more prevalent in schizophrenia compared to healthy controls and other psychiatric disorders. Because of the lack of studies comparing two diagnostic groups we studied NSS in schizophrenia and mood disorders and healthy controls in order to investigate the specificity of NSS for schizophrenia and mood disorders. In our review we found that NSS are also apparent in mood disorders, at intermediate level between schizophrenia and controls (chapter 5). We did find a subset of NSS that did show specificity for schizophrenia compared to mood disorders (chapter 6) but this finding need to be interpreted with caution. We included eye movement disorders in that group and the measurability of these signs is likely to have been poor in the absence of suitable equipment. Moreover the findings await replication in a new dataset before any firm conclusions can be drawn regarding their specificity. In analogy with the poor specificity of the majority of findings in schizophrenia we therefore conclude that generally NSS do not show specificity for schizophrenia although the number of NSS or categories of NSS may differ between diagnostic groups.
SUITABILITY OF NSS AS AN ENDOPHENOTYPE FOR SCHIZOPHRENIA

In this thesis we outlined the three main criteria for the suitability of NSS as an endophenotype for schizophrenia. Regarding measurability we pointed to the main flaws being the diverse composition of the assessments and categories of signs in addition to the less than perfect type of data output. Regarding the reliability we concluded that although the interrater reliability for the categories of signs is acceptable, the interrater reliability for single signs is much worse. In addition there is some evidence suggesting temporal instability of NSS in a specific group of schizophrenia patients, most likely those with a poor outcome (who potentially have a high genetic loading). However the main problem with NSS as an endophenotype is the poor specificity of NSS for schizophrenia. The overall conclusion should therefore be that although NSS continue to show some potential as an endophenotype, the evidence listed here suggests that it is unlikely to provide an endophenotype for schizophrenia.

LIMITATIONS

Several limitations of this thesis must be pointed out. A limitation that our studies share with most studies is its case-control design. Only few longitudinal studies have been published (see chapter 3). All of these studies are naturalistic follow up, with limited (if any) medication change. Since the majority of studies suggest that there are no changes in the number of NSS, studies venturing into establishing this will face issues of power when trying to disprove change in NSS levels.

The power of our study is one of the main problems of this study. As a result of the large number of variables even a substantial sample size as used in these studies has too limited power to effectively control for the extensive numbers of possible confounders. This problem is aggravated by the relative imprecise measure of NSS, which resulted in bigger standard deviations and skewed non-normal distribution and thus further decreased the power. Also we did not include a substantial number of affective psychosis patients in our sample and consequently are unable to investigate NSS in this specific group and particularly the potential differences in NSS in affective psychosis compared to schizophrenia. However, in hindsight the major flaw in the design of this thesis is the lack of information on family history of psychosis of our patients. As a result we were unable to test our hypothesis that an increase of obstetric complications and a need for increased medication at two years follow up are related to differences in family loading for schizophrenia and that NSS are a reflection of vulnerability to schizophrenia.

GENES AND ENVIRONMENT

In an attempt to illuminate the meaning of NSS we will discuss genetic and environmental influences on NSS. Evidence for the association of NSS with genes can be found from several sources. Firstly from twin studies; studies in identical twins and dizygotic twins can provide an estimate of heritability of NSS. However to date only studies in identical twins discordant for
schizophrenia have been published (Cantor Graae et al. 1994; Mosher et al. 1970; Mosher et al. 1971; Niethammer et al. 2000; Stabenau and Pollin 1967; Torrey et al. 21994; Weinberger et al. 1992; Werry et al. 1971). The strongest evidence from twin research comes from the study of Niethammer (2000); they compared identical disconcordant twins with unaffected twins and found the NSS to be increased in the well discordant twins compared to the unaffected twins, a finding consistent with the other studies.

Further evidence can be obtained from family studies in siblings and children of schizophrenia patients (Egan et al. 2001; Flyckt et al. 1999a; Ismail et al. 2000; Kinney et al. 1986; Kinney et al. 1999). Without exception these studies found increased NSS in relatives of schizophrenia patients, compared to subjects without a family history of psychosis. Further evidence for a genetic background may be found in adoption studies and linkage or association studies but to date no such studies have been published. Discussing environment triggers a semantic and theoretical discussion on exactly what can be defined as environmental influence. Medication may be considered an environmental influence, but may also be related to genes. For sake of this discussion we will review environmental influences using a broad definition of environment. Compelling evidence suggests that the number of NSS or at least categories of NSS are subject to fluctuation and influenced by environment. We found the number of neurological signs to be dependent on the number of obstetric complications (see chapter 7). Moreover changes in the number of NSS were present in those patients that had a medication increase at two years follow up. Finally we also found that TD signs, which were included in our NSS assessment, did in fact show a relationship with the type of antipsychotic drug, classical versus atypical. Moreover it is likely that alcohol abuse influences NSS. And finally there are the environmental influences on schizophrenia that may also influence NSS. There is therefore suggestion of both genetic and environmental influences on NSS but any clear relationship has remained obscured. One explanation could be that NSS are a heterogeneous group of symptoms with several neuropathological processes that have separate and often independent relationships that may cross traditional diagnostic boundaries and definitions. However we like to add another possibility as an explanation for the limited progress in the investigation of NSS. The multiple, complex and often contradicting findings in NSS research could be the consequence of gene-environment interaction (GEI). Whereas evidence suggests a GEI between schizophrenia and cannabis abuse, urbanicity, season of birth and obstetric complications this list is far from exhaustive and further research is required into potential candidates such as migration, trauma, adverse life events, maternal deprivation and perhaps NSS.

**FUTURE DIRECTION**

Our findings warrant further investigation of a combination of movement and eye-movement abnormalities as a potential endophenotype for schizophrenia. This would need to include the use of standardised equipment for reducing measurement error. In addition further research in NSS could focus on NSS as a GEI. However, there are several methodological and conceptional issues in the research of GEI that need exploring. Broadly speaking GEI are divided in shared- and non-shared environmental influences. Shared environmental influences are those environmental circumstances that are shared between siblings (for instance social economic status) in contrast to non-shared environmental influences such as trauma. Because of the nature of the
shared environmental influences these are hard to investigate and traditionally the emphasis has been put on non-shared environment. However this is questionable for three reasons. Firstly, there is no reason to assume that environmental factors that are shared are any less influential. Urbanicity is an interesting example in that respect. Its influence is established but will be shared in siblings in the major part of the first two decades of their lives. Secondly because several of the polymorphic alleles that are investigated are extremely common (e.g. 40-50 % for COMT val/val polymorphism) which seems an encouragement to also look at common environmental factors. Finally because the rarity of several non-shared environmental factors in contrast to the commonness of some of the alleles increases the probability of detecting an association with genotypes, but not with environmental exposures. A second problem in the research into GEI is of a more methodological nature and is related to measurement error. Genotyping is in fact much more accurate than the vast majority of methods used to measure environmental exposures. This implies a lower degree of error, which in turn means an easier identification of associations with disease compared to environmental factors.

Broadly 4 methods for further NSS research can be considered. Firstly, the estimation of heritability of non-shared environmental factors in cohorts of identical and fraternal twins can provide insight in GEI for NSS. This method depends heavily on a mathematical approach and the ability to successfully identify and model the appropriate co-variates. Secondly adoption studies can provide a measure for the genetic background of NSS and are particularly interesting because they are able identify GEI with environmental factors that otherwise might been contributed to shared environment (eg urbanicity). Thirdly, an epidemiological approach can be chosen. After the identification of a candidate environmental pathogen and selecting a good candidate gene, the GEI can be tested in a case-control association design. Finally, an interesting approach can be the use of existing (birth) cohorts. This has the advantage that these often provide a wealth of excellent assessment of environment. By genotyping those subjects with a high number of NSS in the (birth) cohorts GEI between environmental factors such as obstetric complications and NSS be successfully tested.

CONCLUSION

Neurological soft signs show multiple and complex relationships with movement disorders, genetic loading for schizophrenia and diagnosis. Because of shortcomings in their measurability, reliability and particularly the specificity of NSS for schizophrenia they are unsuitable as an endophenotype for schizophrenia. However further research into a standardised automated measurement of a combination of movement and eye-movement abnormalities seem warranted. NSS may also provide a tool for the further study of the complex interplay between genes and environment. Considering the parallels and relationships with movement disorders they could thus contribute to the illumination of the role and pathology of movement disorders in schizophrenia and mood disorders.
REFERENCES


ramidal dysfunction induced by neuroleptics? Pharmacopsychiatry. 37, 110-118.
ological and other clinical correlates. J Psychiatr Res. 34, 45-56.
Ismail, B.T., Cantor Graae, E., Cardenal, S., and McNeil, T.F., 1998. Neurological abnormalities in schizophre-
nia: clinical, etiological and demographic correlates. Schizophren Res. 30, 229-238.
Jenyns, L.R., Reeves, A.G., Warren, T., Whiting, R.K., Clayton, R.J., Moore, W.W., Rizzo, A., Tuzun, I.M., 
Bonnett, J.C., and Culpepper, B.W., 1985. Neurologic signs in senescence. Arch Neurol. 42, 1154-
1157.
Keenan, E., O’Donnell, C., Sinanan, K., and O’Callaghan, E., 1997. Severity of alcohol dependence and 
its relationship to neurological soft signs, neuropsychological impairment and family history. Acta 
Psychiatr Scand. 95, 272-276.
signs in chronic schizophrenia. Br J Psychiatry. 158, 770-775.
tients and their families. II. Neurologic and psychiatric findings in relatives. Arch Gen Psychiatry. 43, 
665-668.
sory dysfunction in schizophrenics and their relatives. Schizophr Res. 35, 99-104.
Kolakowska, T., Williams, A.O., Jambor, K., and Ardern, M., 1985. Schizophrenia with good and poor out-
146, 348-357.
719.
Manschreck, T.C., Maher, B.A., and Ader, D.N., 1981. Formal thought disorder, the typetoken ratio and 
disturbed voluntary motor movement in schizophrenia. Br J Psychiatry. 139, 7-15.
in schizophrenic disorders: clinical correlates. Biol Psychiatry. 20, 990-1002.
of sensory soft signs of schizophrenia. Psychopathology. 28, 281-284.
positivenegative dimension in schizophrenia. Biol Psychiatry. 28, 181-192.
Mosher, L.R., Pollin, W., and Stabenau, J.R., 1970. Family studies of MZ twins discordant for schizophrenia: 
Mosher, L.R., Pollin, W., Stabenau, J.R., and Bethesda, M., 1971. Identical twins discordant for schizophre-
nia. Arch Gen Psychiatry. 24, 422-430.
Niethammer, R., Weisbrod, M., Schiesser, S., Grothe, J., Maier, S., Peter, U., Kaufmann, C., Schroder, J., 
cits in schizophrenia: relationship with tardive dyskinesia and negative symptoms. Am J Psychiatry. 
158, 1276-1285.
Sanders, R.D., Keshavan, M.S., and Schooley, R.R., 1994. Neurological examination abnormalities in neuro-
leptic-naive patients with first-break schizophrenia: preliminary results. Am J Psychiatry. 151, 1231-
1233.
Chapter 8


Summary

SUMMARY

With these studies we investigated the meaning of NSS and its potential as an endophenotype for schizophrenia. We looked at the three requirements for a good endophenotype; measurability, reliability and specificity.

The measurability of NSS is compromised by the compositions of debatable categories of NSS. In our literature review we could not find a clear pattern of NSS based on the specificity of NSS for schizophrenia (chapter 5). However the categories of NSS we derived by means of a principle component analysis of those signs distinguishing patients from controls, revealed a pattern of NSS that was related to established abnormalities in schizophrenia but deviated from traditional categories of NSS (chapter 6).

The interrater reliability was measured by rating NSS simultaneously and calculating measures of consistency between raters, which ranged from poor to good for categories of NSS but was good for the overall score (chapter 2). The test retest reliability was studied by looking at the temporal stability of NSS at two years follow up (chapter 3) and the relationship of NSS with medication by means of a cross sectional study (chapter 4). We found no significant changes in the numbers of NSS 2-years after a first episode of psychosis. However, the number of NSS was increased in patients with an increase of medication. These findings concur with the majority of the evidence suggesting that NSS do show temporal stability, but subsets of NSS may show variation related to symptom profile and clinical outcome. The type of medication did not influence NSS insofar they did not incorporate TD signs. However they did influence the number of TD signs. It is therefore likely that NSS are independent from medication insofar the assessments do not incorporate EPS and dyskinesia signs.

We have studied the specificity of NSS by means of a literature review (chapter 5) and case-control study in two diagnostic groups (chapter 6). In our review we found that NSS are also apparent in mood disorders, at intermediate level between schizophrenia and controls. By means of a principle component analysis we did find a subset of NSS that did show specificity for schizophrenia compared to mood disorders (chapter 6) but these findings need to be interpreted with caution. We included eye movement disorders in that group and the measurability of these signs is likely to have been poor in the absence of suitable equipment. Moreover the findings await replication in a new dataset before any firm conclusions can be drawn regarding their specificity. In analogy with the poor specificity of the majority of findings in schizophrenia we therefore conclude that generally NSS do not show specificity for schizophrenia although the number of NSS or categories of NSS may differ between diagnostic groups. The overall conclusion should therefore be that NSS continue to show some potential as an endophenotype and further research into a standardised automated measurement of a combination of movement and eye-movement abnormalities seem warranted. However the evidence listed here suggests that it is unlikely to provide an endophenotype for schizophrenia.

In an attempt to illuminate a potential aetiological environmental influence on NSS we studied the relationship between NSS and obstetric complications (chapter 7). We found the number of neurological signs to be dependent on the number of obstetric complications.
(chapter 7). Another environmental influence may be reflected in changes in the number of NSS in those patients that had a medication increase at two years follow up. These finding could be the result of a gene-environment interaction and further research in NSS could also focus on NSS as a GEI. As such NSS may provide a tool for the further study of the complex interplay between genes and environment. Considering the parallels and relationships with movement disorders they could thus contribute to the illumination of the role and pathology of movement disorders in schizophrenia and mood disorders.
SAMENVATTING
SAMENVATTING

Met deze studies onderzochten we de betekenis van neurologische verschijnselen (Neurologische Soft Signs -NSS) en mogelijkheid om hen als endophenotype van schizofrenie te gebruiken. We toetsten ze daarom aan de kenmerken van een goed endophenotype; meetbaarheid, betrouwbaarheid en specificiteit.

De meetbaarheid van NSS is beperkt door variatie in de samenstelling van groepen van NSS. In onze literatuurstudie vonden we geen patroon van NSS op basis van hun specificiteit voor schizofrenie (hoofdstuk 5). Een indeling gebaseerd op een principale componenten analyse van NSS die gezonde controles van patiënten onderscheidde, onthulde een patroon dat is gerelateerd aan bekende afwijkingen bij schizofrenie. Deze indeling wijkt af van traditionele indelingen van NSS (hoofdstuk 6).

De betrouwbaarheid tussen beoordelaars werd gemeten door de NSS tegelijk door twee onderzoekers te meten en betrouwbaarheidsmaten te berekenen. Deze waren matig tot goed voor de scores op categorieën van NSS en goed voor de totale score van NSS (hoofdstuk 2). De test hertest betrouwbaarheid werd onderzocht door te kijken naar de veranderlijkheid van NSS na 2 jaar (hoofdstuk 3) en de relatie met medicatie met behulp van een studie waar patiënten die verschillende medicatie gebruikten werden vergeleken (hoofdstuk 4). We vonden geen significante veranderingen in het aantal NSS na 2 jaar. Bij de patiënten die meer antipsychotische medicatie hadden gekregen in die 2 jaar was het aantal NSS wel toegenomen. Dit komt overeen met de meerderheid van onderzoeken die suggereren dat NSS stabiel zijn door de tijd afgezet van een subgroep die ernstigere symptomen heeft en een slechte uitkomst van hun ziekte. We vonden ook dat het aantal NSS niet beïnvloed werd door het type antipsychotische medicatie inzover het meetinstrument voor NSS geen tardieve dyskinesie bevatte. Het type medicatie beïnvloede wel het aantal dyskinesie symptomen. Het is daarom aannemelijk dat NSS onafhankelijk zijn van medicatie voor zover ze geen dyskinesie of extrapyramidale symptomen bevatten.

We onderzochten verder de specificiteit van NSS door een literatuurstudie (hoofdstuk5) en een studie die patiënten met schizofrenie en stemmingsstoornissen vergeleek (hoofdstuk 6). In de literatuurstudie vonden we dat NSS ook aanwezig zijn bij stemmingsstoornissen. De aantallen NSS lagen in hoeveelheid tussen schizofrenie en gezonde controles in. Met behulp van de principale componenten analyse vonden we een set NSS die stemmingsstoornissen en schizofrenie onderscheidde onafhankelijk van medicatie. Deze bevindingen moeten voorzichtig geïnterpreteerd worden omdat deze groep ook oogvolgbewegingen als symptoom bevatte die zonder daarvoor geschikte apparatuur gemeten was. Bovendien zal deze bevinding eerst gerepliceerd moeten worden in een andere dataset voordat hier conclusies aan verbonden kunnen worden. In overeenkomst met de matige specificiteit van de meeste bevindingen bij schizofrenie lijkt het daarom waarschijnlijk dat ook NSS niet specifiek zijn voor schizofrenie ondanks het feit dat er wel verschillen gevonden kunnen worden in de hoeveelheid of categorieën NSS. Hoewel NSS dus wel enige potentie als endophenotype blijven behouden is het onwaarschijnlijk dat het als endophenotype kan dienen voor schizofrenie.
Samenvatting

In een poging een mogelijke omgevingsoorzaak van NSS te onderzoeken bestudeerden we de relatie met obstetrische complicaties (hoofdstuk 7). We vonden een relatie tussen het aantal NSS en de aanwezigheid van obstetrische complicaties. Een andere omgevingsinvloed is mogelijk zichtbaar in de toename van NSS in patiënten die na 2 jaar een verhoging hadden van medicatie. Deze bevindingen zouden het gevolg kunnen zijn van een gen-omgeving interactie. Verder onderzoek naar NSS zou zich hierop kunnen richten. Dit zou ook kunnen bijdragen aan kennis over de achtergrond van bewegingsstoornissen gezien de overeenkomsten van NSS en bewegingsstoornissen.
APPENDIX: THE CAMBRIDGE NEUROLOGICAL INVENTORY


Instructions and item descriptions

Overall testing procedure:
Part 1: Assessment of speech; assessment of eye movements; assessment of cranial nerves; Extremity examinations (tone, strength, reflex).
Part 2: Soft sign examinations (primitive reflexes; repetitive movement; sensory integration).
Part 3: Assessment of posture and movements (including catatonia and tardive dyskinesia).

Equipment required: Tendon hammer, tongue depressor, pen, torch, a set of 5-10 small commonly encountered objects (coin, paper clip, match, eraser, rubber band, screw, battery, shell, button).

Instruction: Enter rating in scoring sheet within ( ) space provided. Unless otherwise specified, rate as follows: 0 = normal, 0.5 = sub threshold, 1 = definitely abnormal, 2 = grossly abnormal, 9 = missing, unable to test, or lack of cooperation or comprehension. (Additional description can be entered next to item is advisable if ratings 0.5 or 9 are selected. Do not use rating “2” if a test can only be either positive or negative; such dichotomous items - for example, extensor plantar response – are indicated in the item description.)

Note: If an item is abnormal due to known pre-existent pathology (e.g., sensory neuropathy secondary to diabetes or ophthalmoplegia secondary to thyroid eye disease), then “9” should be rated and an appropriate note made alongside the item.

Part I

Speech
Patient is engaged in casual conversation for up to 3 min. Introduction to the examination and instructions to relax are given.

Poor articulation:
Rate during 3 min of casual conversation. Difficulty in producing phonetically clear speech is rated.
0 - Normally understandable
1 - Patient must repeat to be understood on several occasions
2 - Almost incomprehensible

Aprosodic speech:
Simply unvarying; harsh or stereotyped inflections should not be rated unless marked (e.g., unnaturally loud, strident, high-pitched, or alternatively feeble, whispering, or completely
Appendix

monotonous intonations). Occasionally also automaton-like, singsong, rasping, strangled, or warbling inflections.
0 - No abnormality
1 - Clear loss of normal inflections
2 - Unnatural strange intonations as described above

Unintelligible speech:
Mumbling, non-social speech, self-muttering, not merely due to poor articulation. Do not rate mere incoherent speech due to formal thought disorder.
0 - No abnormality
1 - On few occasions, otherwise can engage in conversation
2 - For more than a substantial period of time (10 min) during interview

Assessment of eye movements
(“I am going to test your eyes next”) There are two main components: (1) smooth pursuit eye movements and (2) saccadic eye movements. Each of the two components should be conducted sequentially and ratings completed afterward.

1. Smooth pursuit eye movements:
Patient is asked to focus on a slowly moving target (e.g., a pencil or pen) at a distance that the patient can focus on. The target is moved slowly in a horizontal and then in a vertical direction. (Examiner: “Could you follow the [e.g., pen] with your eyes, keeping the head still”).

Extent of smooth pursuit eye movements:
Rate as positive if range of movement is clearly restricted. Do not rate if there is obvious proptosis or unilateral ophthalmoplegia.

Smoothness of smooth pursuit eye movements:
Rate as positive if noticeably “catchy” or jerky; only clear instances are rated

Gaze impersistence: Patient is asked to fix his/her gaze on an object (e.g., a pen) at a 45° angle in the horizontal plane of the right and then left visual fields for 15 s each. (Examiner: “Could you keep looking at this [pen] with your head still, until I tell you to stop”).
0 - No deviation from fixation
1 - Deviation from fixation on one or two occasions but able to resume gaze
2 - Deviation from fixation repeatedly; unable to resume gaze

2. Saccadic eye movements: Hold one target at the right extreme of lateral vision and the other target at the left extreme of lateral vision. Patient is asked to look at one of the targets and then quickly at the other (“as fast as possible, to and from for several times”). Observe for smoothness of movement, presence of blinking and head movement. (Examiner: “Could you look at the [pen] and then at this (torch) and back to the [pen]. Do this a few times as quickly as you can”).

Smoothness of saccade movements:
0 - One smooth movement
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1 - Slight jerky movements
2 - Extremely jerky movement

Blink suppression during saccades:
The co-occurrence of blinking is looked for during two horizontal saccades. (Examiner: “I notice you tend to blink while you do this; see if you could do it without blinking”).
0 - No blinks
1 - Unable to stop blinks on occasions even after repeated instruction
2 - Unable to stop blinks on all saccades

Lateral head movements during saccades:
The co-occurrence of lateral head movement (usually in the same direction) with saccades is observed. (Examiner: “You tend to move your head when you do this; see if you could do it without moving the head”).
0 - None
1 - Head moves with eyes, unable to suppress on some occasions even after instruction
2 - Head moves with eyes on all occasions

Selective assessment of cranial nerves.
This part could be completed and scored either item by item or as a unit, depending on the examiner's familiarity with the assessment.

Wink with other eye open: (Examiner: “Could you wink with the other eye open, like this” [Demonstrate].) If lateralized, indicate the side in which unilateral blinking is difficult.

Glabellar tap:
Patient is instructed to fix his/her gaze on a distant point across the room or outside the room. After explanation, the patient is approached from above the forehead outside of the visual field, and the examiner taps the glabellar region 10 times with the index finger. If the spontaneous blink rate is high, the patient is asked to relax, and the blinking pattern is carefully observed before the taps are applied. (Examiner: “I am going to tap your forehead gently. Just try to relax and look ahead at the [fixation point].”) 
0 - One to three blinks (include partial blinks)
1 - More than three blinks with some habituation (reduction of tendency to blink when tapped)
2 - No habituation at all

Rapid tongue movements:
Touch corners of mouth with tip of tongue alternately.[Demonstrate] (Examiner: “Could you stick the tongue out and move it as quickly as you can between the two corners of the mouth.”)
0 - Normal (> 4 touches/s)
1 - Slow (< 4 touches/s)
2 - Very slow or dysrhythmic
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Impersistence-tongue protrusion:
Hold tongue out (without using the teeth) for 15 s. (Examiner: “Could you keep the tongue out until I tell you to stop.”)
0 - Maintains act for 20 s
1 - Retracts tongue before 20 s on one or two occasions but is able to resume test
2 - Retracts tongue before 20 s and unable to complete test

Extremity examinations
These examinations of tone, strength, and reflexes in the upper and lower limbs are performed as a unit with the patient seated. Scores are entered on the page after the entire block of examination.

1. Upper limb examination (Examiner: “I am going to examine your arms next.”)

Upper limb tone:
Flexion-extension, pronation-supination of the elbow joint; and flexion-extension of the wrist joints are examined. The degree of resistance from normal to extreme rigidity (hypertonia) or to extreme flaccidity (hypotonia) is scored. Proper instruction to relax is important. It is advisable that the patient’s arms be moved without any regular rhythm or pattern. (Examiner: “Could you relax and let your arm go as soft as possible while I hold it.”) (Note: Scored for increased tone.)
0 - Normal
1 - Slight to moderate stiffness and resistance
2 - Marked rigidity with difficulty in passive movement

Upper limb strength:
(Examiner: “Could you grasp my fingers as hard as you can.” “Could you pull me toward you”).
0 - Normal
1 - Decreased
2 - Markedly reduced

Upper limb hyperreflexia:
Rating for all reflex items.
0 - Normal
0.5 - Equivocal
1 - Positive
9 - Missing

Upper limb hyporeflexia:
0 - Normal
1 - Reflex absent

2. Lower limb assessment (Examiner: “I am going to examine your legs now. Could you take off your shoes and socks?” This is a good point to observe ambidexterity but the rating can be entered later:
2. Lower limb examination (Examiner: “I am going to examine your legs next.”)

Lower limb tone:
0 - Normal
1 - Definitely increased or decreased
2 - Grossly increased or decreased

Lower limb strength:
(Examiner: “Could you straighten your leg” “Could you point the toes toward you”).
0 - Normal
1 - Decreased

Lower limb hyperreflexia:
0 - Normal
0.5 - Equivocal
1 - Positive
9 - Missing

Lower limb hyporeflexia:
0 - Normal
1 - Reflex absent

Extensor plantar reflex:
The plantar reflex is elicited by a firm stroke on the outer border of the sole with a blunt pointed object (e.g., a key); an extensor response is observed where there is extension of the big toe and outward fanning of the digits.
0 - Normal
0.5 - Equivocal
1 - Extensor

[End of Part 1: This is a good point to allow the patient to have a short break before proceeding to Part 2. Examiner: “Would you like to take a break for a little while?”]

Part 2

Soft signs assessment
There are mainly three groups: The first group of soft sign tests assesses some “primitive reflexes.” The second group is concerned with repetitive sequential motor execution. The third group consists of tests related to integration of sensory information. The patient is seated facing the examiner (seated opposite). Each test is performed and rated before the examiner goes on to the next test.

Snout reflex:
After explanation, the patient is instructed to relax, and the examiner rests a tongue depressor against the patient’s philtrum and taps gently with the index finger. (Examiner: “Could you close your eyes and relax. I am going to tap gently on your mouth.”)
0 - No contraction of the orbicularis orris
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1 - Any contraction of the orbicularis orris

Grasp reflex:
The patient is instructed to relax and the palm is stroked lightly with the examiner's index finger. The sign should be demonstrable at least twice on repetition
0 - No movement of patient's hand
1 - Some flexion of fingers
2 - Examiner's finger grasped

Palmomental reflex:
The patient is instructed to relax. Muscle activity around the lips is observed. The thenar eminence (of the left and then right hand in turn) is then stroked vigorously with a blunt pointed object. Induced movement of the mentalis muscle is observed. If a positive response is gained from either hand, then it is rated as positive. If elicited unilaterally, please indicate in the space provided, the stimulus in which side of the hand led to response in which side of the face.
(Examiner: “I am going to stroke the palm. Could you close your eyes and relax.”)
0 - No movement observed
1 - Movement of the mentalis muscle

Finger-nose test:
The patient is instructed to close eyes and touch the tip of his/her nose with the tip of his/her index finger. (Examiner: “Could you close your eyes and touch your nose with this finger.”)
[Patient's index finger is touched.]
0 - No intention tremor or past pointing
1 - Mild intention tremor or past pointing
2 - Marked intention tremor or past pointing

Finger-thumb tapping:
The patient is asked to touch tip of thumb with tip of index finger as quickly as possible.
(Examiner: “Could you do this? [Demonstrate]. Now start.”)
0 - Normal
1 - One or two minor mistakes, slow (< 11s) or clumsy (e.g., gross presence of associated movements in other parts of the hand and forearm), but no major disruption of movements
2 - Major disruption (e.g., total loss of rhythm or precision) or repeated breakdowns of sequence

Finger-thumb opposition:
The patient is asked to place both hands palm up with fingers fully extended on his/her legs. The patient is to start with his/her dominant hand and is to touch the tip of his/her fingers with the tip of his/her thumb, from index finger to little finger, returning to index finger, for a total of 10 repetitions. Examiner: “Now could you do this [demonstrate] and repeat 10 times. Start now.” [Observe for mirror movement.]
0 - Normal
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1 - One or two minor mistakes, slow (< 11s) or clumsy (e.g., gross presence of associated movements in other parts of the hand and forearm), but no major disruption of movements
2 - Major disruption (e.g., total loss or rhythm or precision) or repeated breakdown of sequence

Mirror movements (1):
The patient's hand, which is not performing the finger-thumb opposition test, is observed for mirror movements (tendency for the resting hand to move in a way symmetrical to the performing hand)
0 - No observable movement
1 - Minor movements of the fingers
2 - Consistent, distinctive movements of the fingers

Diadochokinesis:
The patient is asked to make a fist with one hand and pat the back of the fist with the other hand alternately using the palm and the dorsum. Demonstrate five times; rate as finger-thumb opposition
0 - Normal
1 - One or two minor mistakes, slow (< 11s) or clumsy (e.g., gross presence of associated movements in other parts of the hand and forearm), but no major disruption of movements
2 - Major disruption (e.g., total loss of rhythm or precision) or repeated breakdown of sequence

Mirror movements (2):
During the test for dysdiadochokinesia, the patient's resting hand, holding a fist, is observed for mirror movements (pronation-supination).
0 - No observable movement
1 - Minor pronation or supination movements
2 - Consistent, distinctive pronation and supination movements of the forearm

Fist-edge-palm test:
The patient is shown the task and then asked to perform the following: using a smooth and steady rhythmic pattern, to touch the table with the side of his/her fist, the edge of his/her hand, and the palm of his/her hand. The patient is to break contact with the surface of the table between each change in hand position, but not to bring the arm back in full flexion. The patient is to repeat this sequence of position changes 10 times. (Examiner: “Watch me do this.” [Demonstrate five times, without verbal instruction.] “Now see if you can do it.” [Repeat demonstration once if patient fails to perform.])
0 - Normal
1 - One or two minor mistakes, slow or clumsy (e.g., gross presence of associated movements in other parts of the hand and forearm), but no major disruption of movements
2 - Major disruption (e.g., total loss of rhythm or precision) or repeated breakdowns of sequence
Appendix

Oseretsky test:
The patient is to place both hands on the table, one hand palm down and the other hand in the shape of a fist. The patient is then asked to simultaneously alternate the position of his/her hands in a smooth and steady motion. The patient is asked to repeat this motion 15 times. Synchrony in change of position is observed. (Examiner: “Watch me do this.” [Demonstrate five times.] “Now see if you can do it.” [Repeat demonstration once only if patient fails to perform.])

0 - Normal
1 - Minor mistakes, but no major desynchronization of movements
2 - Total desynchronization or repeated breakdown of sequence

Rhythm-tapping test:
Ask the patient to reproduce exactly the series of taps heard while the patient has eyes closed (five trials using stimulus sequence suggested). (Examiner: “I am going to tap some sound on the table like this; some taps are louder than others [demonstrate]. Could you tap the same rhythm back to me? Now close your eyes and listen.”)

<table>
<thead>
<tr>
<th>Stimulus sequence</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>. * * * * . *</td>
</tr>
<tr>
<td>2</td>
<td>. * . * . *</td>
</tr>
<tr>
<td>4</td>
<td>* . . * . . *</td>
</tr>
<tr>
<td>5</td>
<td>. . * . . *</td>
</tr>
</tbody>
</table>

. = light tap; * = loud tap. Horizontal distance between taps corresponds to length of pauses.

0 - No error
1 - One error (either in loudness or rhythm)
2 - Two or more errors

Go/no-go test:
The patient is asked to tap the table once if the examiner taps the table once, but not to tap if the examiner taps the table twice. Give adequate demonstration and practice to ensure comprehension of task. Before proceeding, the examiner asks the patient to describe what he/she is supposed to do. (Examiner: “If I tap once on the table like this [demonstrate], could you tap once. If I tap twice on the table like this [demonstrate], please do not tap.”)

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>* *</th>
<th>*</th>
<th>*</th>
<th>**</th>
<th>*</th>
</tr>
</thead>
</table>

Response

0 - No error
1 - One error
2 - Two or more errors

Extinction:
The patient is seated, with hands resting palm down, on his/her knees and with eyes closed. The patient is told that he/she will be touched on the cheek, the hand, or both and that he/
she is to say where he\she has been touched. If the patient names just one touch, he\she is asked (the first time this occurs only) if a touch is felt anywhere else. Simultaneous touching is performed in the following order: right cheek-left hand, left cheek-right hand, right cheek-right hand, left cheek-left hand, both hands, and both cheeks. Intact sensation to touch is confirmed in each test area beforehand. (Examiner: “I am going to touch your face and your hand like this [demonstrate]. Could you tell me which side of the face and the hand I am touching? For example ... [demonstrate]. Now close the eyes.”)

0- No error
1- One error
2- Two or more errors

Finger agnosia:
With the patient facing the examiner, hands palm down on the table, fingers spread, and eyes closed, the examiner simultaneously touches two of the patient’s fingers. The patient is asked to state the number of fingers between the two touched. The answer may be 0, 1, 2, or 3. A total of five trials for each hand is tested. See scoring sheet for test sequence: 1 for thumb, 5 for last finger, etc. (Examiner: “Could you put your hand on the table like this [demonstrate]. I am going to touch two of the fingers like this [demonstrate]. I’d like you to tell me how many fingers there are in between the ones that I am touching. For example, this will be ... [demonstrate]. Now close your eyes.”)

0- No error
1- One error
2- Two or more errors

Stereognosis:
The patient, with eyes closed, is asked to identify an object placed in his\her hand. The patient is instructed to feel the object with one hand and to take as much time as needed. If the patient cannot name the object, he\she is asked to describe for what purpose the object is used. The patient starts with the dominant hand. Five trials are conducted for each hand. Objects are placed between thumb and index fingers for patients, with proper care being taken to ensure that the patient does not look at the object. Suggested objects are: paper clip, coin, rubber band, eraser, screw, small seashell, or match). (Examiner: “Could you close your eyes and tell me what this object is, just by feeling it.”)

0 - No error
1 - One error
2 - Two or more errors

Graphesthesia:
The patient, with eyes closed, is asked to identify the number written on his\her palm with a blunt point, the number being orientated facing the patient. Five trials for each hand. Stimulus can be repeated once upon request by the patient or when the patient gives a response other than a number (Examiner: “I am going to trace a number on your palm; for example, this would be a [number].” [Demonstrate.] “Could you tell me what the number is, with your eyes closed.”)

0 - No error
1 - One error
Appendix

2 - Two or more errors

Left-right orientation:
[The examiner should remove wristwatch before the test] The patient is asked to point to his/her right foot, left hand; place his/her right hand to left shoulder, left hand to right ear; point to the examiner's left knee, then right elbow; with examiner's arms crossed, point to examiner's left hand with his/her right hand, and with examiner recrossing arms, point to examiner's right hand with his/her left hand. (Examiner:”Could you point to - with your-. “)

0 - No error
1 – Left/right disorientation confined to perception of another person
2 – Left/right disorientation in self-body space

[End of Part 2: Another break can be taken at this point. Examiner: “Would you like to take another break now?”

Part 3

Posture and gait assessment
These assessments are completed first with the patient seated, then standing up, and finally walking. The examinations are most conveniently completed as a unit before scores are entered. If the examiner is unfamiliar with the assessment, the examination could be divided into three smaller subunits (see below), each to be carried out as a block. It is important, however, that ratings for global items such as dyskinetic movements be entered after the examiner has observed the patient perform in all three blocks. The recommended sequence of examination is divided into Blocks A, B, and C.

Block A: (1) The patient has been observed during the preceding parts of the assessment for global items such as perseveration, echopraxia, and mutism. (2) The patient is seated in a chair with his/her hands on knees, with legs slightly apart, and with feet flat on the floor. [Observe involuntary movement in the entire body.] (3) The patient is asked to sit with his/her hands hanging unsupported (if the patient is male, with hands between legs; if the patient is a female, with hands hanging over knees). [Observe involuntary movements in hands and body.] (4) The patient is asked to open his/her mouth. [Observe involuntary tongue movement.] (5) The patient is asked to protrude tongue. [Observe involuntary movement.] (6) The patient is asked to tap thumb with each finger as rapidly as possible for about 15 s, first with the left and then the right hand. [Observe involuntary movements of face and legs.]

Block B: (7) The patient is asked to stand up.[Observe posture.] (8) The patient is asked to hold extended arms horizontally in front and then to have the eyes closed. [Observe pronator drift, tremor, and Romberg's sign.] Then the extended arms are moved to the side, and instruction is given, with demonstration, to drop the arms to the sides of the body. [Observe arm dropping and imposed posture.] (9) The examiner instructs the patient to let the arms go loose and then moves the patient's arms into various positions, at times releasing support and noting whether the arms drop freely (imposed posture and gegenhalten). (10) The examiner raises each of the patient's outstretched arms in turn with one finger after instructing the patient to
resist this. [Test for mitgehen.] (11) The examiner pats the sides of his own legs, then taps his own chest, and then scratches his own head after first instructing the patient to stand with arms by sides. [Test for echopraxia.]

**Block C** (12) The patient is asked to balance himself for 15 s on each leg in turn. (13) The patient is instructed to walk a few steps, stop, and return [observe gait, etc.]. (14) Tandem walking [see item description].

Gait (exaggerated associated movement):
Excess arm, leg, or trunk movement observed during walking.
0 - Absent
1 - Definitely present
2 - Markedly or pervasively present

Gait (reduced associated movement):
Reduced arm, leg, or trunk movement observed during walking.
0 - Absent
1 - Definitely present
2 - Markedly or pervasively present

Slow/shuffling gait:
Typical parkinsonian gait rated.
0 - Absent
1 - Definitely present
2 - Markedly or pervasively present

Manneristic/bizarre gait:
Mere clumsy or lumbering gaits should not be rated, and gait should be idiosyncratic rather than haunched, lordotic, or shuffling - for example, constrained, mincing, overprecise; or alternatively extravagant, overelaborate, featuring interpolated movements such as sidesteps and bowing. Also bizarre crablike, crouching, or anthropoid gaits, and those with multiple, not easily described abnormalities.
0 - Absent
1 - Definitely present
2 - Markedly or pervasively present

Dyskinetic face and head movement:
Simple brief dyskinesia-like, including chorea. Do not rate tongue movements unless they also involve the mouth or the jaw.
0 - Absent
1 - Definitely present
2 - Markedly or pervasively present
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Sustained face and head movement:
Simple sustained grimace-like. Do not rate tongue movements unless they also involve the mouth or the jaw (e.g., spasmodic facial contortions); should not be completely fixed.

Complex face and head mannerism/stereotypy:
Complex mannerism/stereotypy-like (usually of head; e.g., turning away, side-to-side looks, searching movements).

Gegenhalten:
Resistance to passive movement which increases with the force exerted. Typically has a "springy" quality and appears automatic rather than willful. May be restricted to just one muscle group. Resistance increases with increasing force.

Mitgehen:
"Anglepoise lamp" raising of arm in response to light pressure, in the presence of an apparent grasp of the need to resist; should be demonstrable repeatedly. Severity of rating depends on the rapidity and apparent wish to anticipate the movement. Do not rate if understanding of instruction is poor.

Simple abnormal posture:
posture while standing.
0 - Normal
1 - Somewhat stooped
2 - Very stooped with downward gaze or rigid and extended

Complex abnormal posture:
Mere ungainliness or slouching should not be rated.
0 - Normal
1 - Assuming, for example, obviously abnormal hunched, constrained “closed” or alternatively exaggeratedly slack, overrelaxed positions when sitting; hugging sides, twisting legs round each other, sitting with torso forward but legs to one side in extremely uncomfortable way.
2 - Marked or pervasive posturing. For example: while sitting, repeatedly hunching forward and rocking; while standing or walking, striking a succession of poses.

Persistence of imposed postures:
This is tested while testing tone of upper limb. If abnormality is suspected, further testing is carried out, positioning the patient’s limbs and releasing them.
0 - Normal
1 - Not sustained: tendency to retain limb positions passively imposed during testing for at least several seconds; this should be observed more than once.
2 - Sustained “waxy flexibility”

Dyskinetic trunk/limb movement:
Simple brief dyskinesia-like (e.g., stamping movements of legs, rocking trunk movements). Specify: random/irregularly repetitive/rhythmic-like; including rocking and chorea.
Dystonic trunk/limb movement:
For example, dystonic posturing of extremities, hyperpronation on arm raising, torsion movements.

Trunk/limb mannerism/stereotypy:
More stereotypy-like - for example, rubbing the thumb over the forefinger; other kinds of finger play; touching, rubbing, stroking, and patting various parts of the body, especially the face. Also repeatedly turning the head away from the examiner, looking round distractedly throughout the interview, twisting one arm up behind the back while walking, and repeatedly rising from chair to approach the examiner. More mannerism like - for example, holding arms in an unnatural crooked way, holding an arm out in a meaningless gesture, and keeping one arm tucked under armpit.

Arm drift:
Patient asked to hold two arms straight in front of him/her horizontally and close the eye. Downward drift of one or both of the arms is observed. (Examiner: “Could you hold your arms out in front of you, like this [demonstrate]. Now close your eyes and keep the arms in the same place.”)

Arm dropping:
The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard, and there is a slight, natural rebound as the arms hit the sides. If the sign is positive, the arms fall very slowly. (Examiner: “Now relax and let the arms drop to the sides like this [demonstrate].”)
0 - Normal, free fall with loud slap and rebound
1 - Fall slowed with less audible contact and little rebound
2 - Arms fall as though against resistance; as though through glue

Tremor (postural):
Rated with patient’s arms outstretched. Typical resting, low frequency, parkinsonian “pill-rolling” tremor rated.
0 - No tremor
1 - Mild or occasional tremor
2 - Gross or persistent tremor

Tremor (resting):
Rated with patient’s arms by the side. Typical resting, low-frequency, parkinsonian “pill-rolling” tremor rated.
0 - No tremor
1 - Mild or occasional tremor
2 - Gross or persistent tremor

Romberg’s sign:
Standing with eyes closed and feet together.
0 - Normally still or slight weaving
1 - Widened base to stay in place
2 - Unable to stand still with eyes closed

Balance on one leg: Stand on one leg with eyes open for 10 s.
0 - No difficulty
1 - With great difficulty
2 - Unable to perform

**Rate irrespective of side**

**Walking:**
Walking down the hall at least five paces. Other abnormalities not previously rated: e.g., spastic, hemiplegic gait.

**Tandem walking:**
Heel to toe for 10 paces.

**Abrupt/rapid spontaneous movement:**
For example, sudden gestures, acts carried out smartly, springs to attention when asked to stand.

**Slow/feeble spontaneous movement:**
Weak, languid, labored movements

**Exaggerated movements:**
Accompanied by flourishes/flurries of adventitious movements

**Iterations of spontaneous movements:**
Gestures or mannerisms repeated over short space of time: e.g., touching face and then repeating this several times; manneristically smoothing hair, then repeating this with increasing force until striking head; touching ring finger on one hand (while alluding to ring being stolen), then doing the same on the other hand, then repeating the whole sequence.

**Ambitendence:**
For example, extending arm when examiner’s arm is proffered; halting in mid-action and moving arm to one side; while walking, stopping, half-turning back, and then continuing.

**Mutism:**
Global rating for entire interview.
0 - No mutism
1 - Fewer than 10 isolated words in whole interview
2 - No speech

**Neck rigidity:**
Range of neck movement is gently tested with patient seated, after explanation.
0 - Absent
1 - Definitely present
2 - Markedly or pervasively present
Appendix

Overactivity:
[Do not rate simple restlessness]

Akathisia;
[do not rate unless substantial.] Typically bizarre rather than resembling simple restlessness; akathisia should be excluded where suspected.
0 - Absent
1 - Continual motor unrest: e.g., crossing and uncrossing legs, looking around, half rising from the chair; executing unending series of manneristic actions, touching body, then clasping hands, then gripping the chair arm, etc.
2 - Approaching catatonic excitement: in more or less constant motion, incessantly performing pointless actions, which are reiterated, elaborated, and transformed into one another: e.g., touching cardigan, then moving hands up and down the edges, then unbuttoning cardigan and buttoning it up again, followed by breaking off interview to clamber over the tables and chairs on the ward. Also full-blown excitement: e.g., patient who moved round and round the ward, striking an endless series of quasi-symbolic poses.

Underactivity:
[Do not rate if the patient is clearly sedated]

Parkinsonian;
[do not rate unless substantial.] Some degree of abnormality is commonly observed and should not be rated unless very noticeable.
0 - Absent
1 - Sits abnormally still throughout the interview with hardly any postural shifts; slumped in chair; very passive.
2 - Marked hypokinesia, generally with striking absence of postural adjustments: e.g., sitting perched on chair in same position throughout interview, not turning head when addressed from different direction; always sitting in same place on ward with arms in praying position. Also full-blown stupor if encountered.

Automatic obedience:
May take the form of exaggerated cooperation with instructed movements: e.g., when asked to lift a finger, whole arm raised; when arm reached for, whole body leant forward and turned toward examiner; holding out both hands when examiner’s hand is offered for shaking. Alternatively, spontaneous continuation of actions: e.g., flapping arms when asked to drop them to sides; actively continuing passive arm movements during examination for tone. Occasionally, complying with all requests to an extraordinary degree: e.g., patient who screwed up eyes when asked to close them; peered intently in caricatured way when asked to look out of window; when asked to keep head up while walking, proceeded across the room with neck hyperextended.

Poor/feeble compliance: Inability to perform requested actions not explained by poor understanding, general uncooperativeness
Appendix

Blockinglambitendence, or parkinsonism; often has a bizarre quality - e.g., when raising arm, movement gradually dies away; carries out most instructions promptly but fails to comply with some; cannot seem to maintain arms outstretched; when asked to hold out arms, only seems able to do so in halfhearted, crooked way; when asked to raise a finger, after some delay lifts thumb.

Other abnormal behavior:
Specify negativism hypermetamorphosis. Do not rate any other abnormality than these.

Negativism:
Should always reflect concrete instances rather than indefinite attitude - e.g., pulling arm violently away whenever the examiner reaches for it, holding breath when asked to breathe deeply, shutting eyes tightly when approached with an ophthalmoscope, or jumping up when asked to lie down. Also, taking off socks when told to put shoes on; getting up from customary reclining position and walking away whenever approached by examiner. Occasionally, domination of entire behavior by bizarre contrariness: e.g., normally quiet patient who met attempts to examine him with immediate struggling and vilification; leant backwards when pulled forwards; refused to stand up and then refused to sit down again.

Hypermetamorphosis:
Typically only seen in setting of marked overactivity - e.g., attention repeatedly drawn by specks, bits of fluff, etc., on the floor, which are reached for and scrutinized; randomly approaching various objects, including wastebasket, rummaging in it, extracting apple core, and eating it.
0 - Absent
1 - Definitely present
2 - Markedly or pervasively present

Echophenomena:
Tendency to repeat the examiner’s speech or mimic the examiner’s action.

Echopraxia:
Incomplete copying movements should not be rated, and exercise judgment as to whether patient is just trying to be helpful. As well as being merely copied, movements may be modified or amplified: e.g., smoothing of hair substituted for examiner’s scratching of head, echopraxic chest patting progressively exaggerated until patient pulling at his shirt.

Global rating for echophenomena:

Perseveration:
Tendency to persist in a particular response after it ceased to be appropriate.
Global rating for perseveration
[End of examination]
NEUROLOGICAL SOFT SIGNS ASSESSMENT SCORE SHEET

Patient:  
Number:  
Rater:  
Date:  

Instruction: Enter rating in scoring sheet within ( ) space provided. 
Unless otherwise specified, rate as follows: 
0 - Normal 
0.5 - Subthreshold 
1 - Definitely abnormal 
2 - Grossly abnormal 
9 - Missing. Or unable to test, lack of cooperation or comprehension 
Additional description can be entered next to rating in the space provided. Additional information is advisable if a rating of “0.5” or “9” is selected. Do not use rating “2” if a test can only be either positive or negative; such dichotomous items (e.g., extensor plantar response) are indicated in the item description.

Part 1 Score sheet
Articulation ( )
Aprosodic ( )
Unintelligible ( )
Extent of smooth ( )
pursuit eye movements ( )
Smoothness of smooth ( )
pursuit eye movements ( )
Impersistent gaze ( )
Saccade smoothness ( )
Saccade blink suppression ( )
Saccade head movements ( )
Wink ( )
Glabellar tap ( )
Rapid tongue movements ( )
Impersistent tongue protrusion ( )
Extensor plantar reflex (left) ( )
Extensor plantar reflex (right) ( )
Appendix

Extremity examination

<table>
<thead>
<tr>
<th></th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Limb increased</td>
<td>left</td>
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<td></td>
<td>right</td>
</tr>
<tr>
<td>Upper limb decreased</td>
<td>left</td>
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<tr>
<td></td>
<td>right</td>
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<tr>
<td>Lower limb increased</td>
<td>left</td>
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<tr>
<td></td>
<td>right</td>
</tr>
<tr>
<td>Lower limb decreased</td>
<td>left</td>
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<tr>
<td></td>
<td>right</td>
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</table>

*Part 2 Score sheet*

<table>
<thead>
<tr>
<th>Reflex</th>
<th></th>
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<tbody>
<tr>
<td>Snout reflex</td>
<td>( )</td>
</tr>
<tr>
<td>Grasp reflex</td>
<td>( )</td>
</tr>
<tr>
<td>Palmomental reflex</td>
<td>( )</td>
</tr>
<tr>
<td>Laterality of palmomental reflex</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hand stimulated</th>
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</thead>
<tbody>
<tr>
<td>Chin response</td>
<td>left</td>
</tr>
<tr>
<td></td>
<td>Left</td>
</tr>
<tr>
<td></td>
<td>Right</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Finger-nose test (left)</td>
<td>( )</td>
</tr>
<tr>
<td>Finger-nose test (right)</td>
<td>( )</td>
</tr>
<tr>
<td>Finger-thumb tapping (left)</td>
<td>( )</td>
</tr>
<tr>
<td>Finger-thumb tapping (right)</td>
<td>( )</td>
</tr>
<tr>
<td>Finger-thumb opposition (left)</td>
<td>( )</td>
</tr>
<tr>
<td>Finger-thumb opposition (right)</td>
<td>( )</td>
</tr>
<tr>
<td>Mirror movements (left)</td>
<td>( )</td>
</tr>
<tr>
<td>Mirror movements (right)</td>
<td>( )</td>
</tr>
<tr>
<td>Diadochokinesia (left)</td>
<td>( )</td>
</tr>
<tr>
<td>Diadochokinesia (right)</td>
<td>( )</td>
</tr>
<tr>
<td>Mirror movements (left)</td>
<td>( )</td>
</tr>
<tr>
<td>Mirror movements (right)</td>
<td>( )</td>
</tr>
<tr>
<td>Fist-edge-palm test (left)</td>
<td>( )</td>
</tr>
<tr>
<td>Fist-edge-palm test (right)</td>
<td>( )</td>
</tr>
<tr>
<td>Oseretsky test (left)</td>
<td>( )</td>
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<td>Oseretsky test (right)</td>
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### Rhythm tapping test

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Response</th>
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<tbody>
<tr>
<td>1</td>
<td>** * * * * *</td>
</tr>
<tr>
<td>2</td>
<td>. * . * . *</td>
</tr>
<tr>
<td>3</td>
<td>* . . * . . *</td>
</tr>
<tr>
<td>4</td>
<td>* . . * . *</td>
</tr>
<tr>
<td>5</td>
<td>. . * . . *</td>
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</tbody>
</table>

. = light tap; * = loud tap. Horizontal distance between taps corresponds to length of pauses.

### Golno-go test

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>* * * * ** *</th>
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<tbody>
<tr>
<td>Response</td>
<td></td>
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</table>

### Extinction

<table>
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<tr>
<th>Stimulus</th>
<th>Right cheek</th>
<th>Left cheek</th>
<th>Right cheek</th>
<th>Left cheek</th>
<th>Right hand</th>
<th>Right cheek</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulus</td>
<td>Left hand</td>
<td>Right hand</td>
<td>Right hand</td>
<td>Left hand</td>
<td>Left hand</td>
<td>Left cheek</td>
</tr>
<tr>
<td>Response</td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Finger agnosia (left)

| Left-hand response | 2-4 | 1-3 | 3-4 | 2-5 | 1-5 |

| Right-hand response | 1-3 | 2-4 | 1-4 | 2-3 | 1-5 |

### Stereognosia (left)

| Left-hand response | 3   | 7   | 8   | 5   | 9   |

| Right-hand response | 2   | 4   | 0   | 3   | 6   |

### Left-right orientation

<table>
<thead>
<tr>
<th>Point to Your right food</th>
<th>Your right hand</th>
<th>Your left hand</th>
<th>Your right shoulder</th>
<th>Your right ear</th>
<th>My left knee</th>
<th>My right elbow</th>
<th>My left hand</th>
<th>My right hand</th>
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</thead>
<tbody>
<tr>
<td>With</td>
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</table>
Appendix

**Part 3 Score sheet**

Gait - increased movement ( )
Gait - decreased movement ( )
Gait - shuming ( )
Gait - manneristic ( )
Facial dyskinesia ( )
Face, head movement -sustained ( )
Face, head movement, complex/stereotypy ( )
Gegenhalten ( )
Mitgehen ( )
Simple abnormal posture ( )
Complex abnormal posture ( )
Imposed posture persistence ( )
Trunk-limb dyskinesia ( )
Trunk-limb dystonia ( )
Trunk-limb mannerism ( )
Standing ( )
Arm drift ( )
Arm dropping ( )
Tremor (postural) ( )
Tremor (resting) ( )
Romberg’s sign ( )
Balance (left) ( )
Balance (right) ( )
Walking ( )
Tandem walking ( )
Abrupt spontaneous movement ( )
Slow spontaneous movement ( )
Exaggerated movements ( )
Iterative spontaneous movements ( )
Ambitendency ( )
Mutism ( )
Neck rigidity ( )
Overactivity ( )
Underactivity ( )
Automatic obedience ( )
Noncompliance ( )
Other abnormal behavior ( )
Echophenomena ( )
Perseveration ( )
CURRICULUM VITAE

Marco PM Boks (1966) studeerde geneeskunde aan de Rijksuniversiteit Groningen en speciali-
seerde zich tot psychiater in het Academisch Ziekenhuis Groningen. In 1997 startte hij zijn pro-
motieonderzoek; Neurological soft signs in schizophrenia and mood disorders: Investigating a
potential endophenotype. Na het voltooien van zijn opleiding in 2001 werkte hij als consultant
psychiatrist bij de Nottinghamshire Healthcare Trust (UK) en als associate researcher bij de
Mind, Brain and Behaviour groep van Peter Liddle bij de University of Nottingham. Daar werkte
hij aan onderzoek naar Event Related Potential en fMRI verschillen tussen patiënten met een
bipolaire stoornis en schizofrenie. Sinds 2003 werkt hij bij het UMC Utrecht en richt zich daar
in het bijzonder op de genetische verschillen tussen de bipolaire stoornis en schizofrenie. Voor
meer informatie over zijn huidige werk; www.psychiatrischegenetica.nl.
DANKWOORD
DANKWOORD

In gedachten heb ik dit dankwoord al vele malen herschreven. Zo heb ik bijvoorbeeld overwogen in plaats van een dankwoord een gedicht te plaatsen over de ijdelheid en schoonheid van de wetenschap of mij te beperken tot een lijst met namen al dan niet in willekeurige volgorde. Want wie moet ik noemen in mijn dankwoord? Waar begin je en waar houd je op? Bij de juffrouw van de lagere school die mij de eerste ervaringen gaf dat leren leuk kan zijn? Mijn ouders die me tot een steun waren en zijn? Casper, Merijn en Herma van wie ik veel houd? Ontegenzeggelijk hebben Casper en Merijn met hun (meestal) blijmoedige gemoed mij op veel momenten energie gegeven. Herma, heeft mij daarnaast enorm geholpen de balans tussen werk en ontspanning te behouden.

Als ik me beperk tot mijn wetenschappelijke loopbaan moet ik beginnen met professor Van den Hoofdakker en professor Ormel, die mij als jonge enthousiaste student hielpen mijn wens iets wetenschappelijks te doen vorm te geven. Direct gevolgd door Rob van den Bosch en Rikus Knegtering. Het was in mijn keuzejaar van de opleiding dat ik mij realiseerde dat onderzoek doen in de psychiatrie mij de mogelijkheid gaf mijn exacte kennis en fascinatie voor het brein en de psyche te combineren. Rob van den Bosch ben ik in het bijzonder dankbaar voor zijn geduld met mijn ongedurigheid. Rikus Knegtering voor zijn bereidheid en vermogen om het onderzoek te bespreken in de context van recente ontwikkelingen in het schizofrenie onderzoek. Ik denk dat ons laatste telefonische 5-minuten gesprek de cohesie en diepgang van mijn proefschrift aanmerkelijk heeft bevorderd.


This thesis would not have been possible without the help of my English colleagues. I particularly like to thank professor Peter Liddle for teaching me a step-wise approach in analysing data. Working with him has truly been an inspiring experience. Stuart Leask I like to thank, not only for being a collaborating and excellent researcher, but also for being a friend and supportive colleague. I am looking forward to extending our collaborations.
Dankwoord

Als laatst maar niet op de minste plaats wil ik de patiënten en familie die aan dit onderzoek deelnamen, in vaak moeilijke omstandigheden voor henzelf, hartelijk bedanken. Niet alleen zijn zij door hun deelname onmisbaar, maar zij vormen ook uiteindelijk mijn inspiratiebron voor onderzoek.