BACKGROUND

Ever since the introduction of the diagnosis of dementia-praecox by Kraepelin 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 verzeichnen, 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 the 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). A problem when investigating NSS in schizophrenia is the fact that numerous differences in
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 syndromes 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, extrapyramidal signs (EPS) and catatonia. In the Cambridge Neurological Investigation (CNI) (Chen et al. 1995) a category for catatonia, tardive dyskinesia and for extrapyramidal 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. 1991; 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 (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 aetiological environmental influence on NSS we studied the relationship between NSS and obstetric complications (chapter 7).
REFERENCES


Introduction


