Are neurological soft signs pre-existing markers in individuals with an at-risk mental state for psychosis?

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Abstract

Background and Aims: Neurological soft signs (NSS) are more common in schizophrenic psychoses and in genetically high-risk individuals than in healthy controls. But nothing is known so far regarding individuals with a clinical at-risk mental state (ARMS). The goals of our study therefore were a) to compare the NSS frequency in ARMS individuals to that of first-episode psychosis (FEP) patients; and b) to test whether NSS could predict the transition to psychosis.

Methods: Neurological soft signs were assessed using a shortened version of the Neurological Evaluation Scale (NES). Fifty-three ARMS individuals (16 with later transition to psychosis = ARMS-T, and 37 without transition = ARMS-NT) and 27 FEP patients were recruited through the Basel Early Detection Clinic *FePsy*.

Results: Of the FEP patients 37% showed NSS. We found no significant differences between FEP and ARMS-T patients or between ARMS-NT and ARMS-T.

Conclusions: Our findings of NSS being present already before transition to psychosis to the same extent as after transition provide further support to the neurodevelopmental hypothesis of schizophrenic psychoses. Furthermore, our findings might indicate that ARMS-NT individuals also suffer from some sort of neurodevelopmental abnormalities.

Key words: schizophrenic psychoses, at-risk mental state, transition to psychosis, neurological soft signs, trait-marker, neurodevelopmental disorder

1. Introduction

Neurological soft signs (NSS) are minor abnormalities in sensory integration, motor coordination, and sequencing of complex motor acts often manifesting themselves in patients with schizophrenia or schizophrenia-spectrum disorders (Heinrichs and Buchanan, 1988). They have also been reported in other neuropsychiatric disorders, such as chronic posttraumatic stress disorder (Gurvits et al., 2000), bipolar disorder (Negash et al., 2004), obsessive compulsive disorder (Mergl and Hegerl, 2005) as well as in patients suffering from neurodegenerative diseases (Chan et al., 2011). However, their prevalence has been shown to be higher in schizophrenia than in other psychiatric disorders (Cox and Ludwig, 1979; Jaafari et al., 2011).

In the last two decades, NSS have been studied in patients with chronic schizophrenia (King et al., 1991), first-episode schizophrenia (FEP) (Dazzan and Murray, 2002; Peralta et al., 2011) and in individuals with a high genetic risk for schizophrenia (Lawrie et al., 2001). Evidence suggests that NSS are more common in chronic schizophrenia and FEP patients than in healthy controls (King et al., 1991; Rossi et al., 1990). In the largest study to date, 78% of first episode antipsychotic-naïve patients showed at least one neurological abnormality (Peralta et al., 2011). NSS were also found to be more frequent in nonpsychotic genetically high-risk individuals with at least two first- and/or second-degree relatives with schizophrenia than in healthy controls (Gourion et al., 2004; Lawrie et al., 2001). Furthermore, in groups of normal volunteers, individuals presenting higher schizotypy showed significantly more soft signs as expressed by higher “Neurological Evaluation Scale” (NES) total scores and higher "Sequencing of Complex Motor Acts” and “Other Soft Signs” subscale scores (Barkus et al., 2006; Mechri et al., 2010; Theleritis et al., 2012).

Neuroanatomical correlates of NSS were extensively investigated in *healthy individuals.* They seem to be associated with decreased volume of the inferior frontal gyrus, middle and superior temporal gyrus, and anterior cingulate gyrus (Dazzan et al., 2006). In FEP patients, an excess of NSS has been found to be associated with reduced brain volume in subcortical (basal ganglia, thalamus and cerebellum) and frontal cortical areas (premotor area, frontal gyrus), independent of antipsychotic medication (Dazzan et al., 2004; Janssen et al., 2009; Thomann et al., 2009). These regions, known to play a key role in sensory and motor integration may thus represent the neuroanatomical substrate of NSS, at least in psychotic patients. The fact that NSS in non-psychotic and psychotic individuals have partially different anatomical correlates may indicate that different pathogenic mechanisms are responsible for the presence of NSS in different populations (Thomann et al., 2009).

It has been hypothesized that early damages of the central nervous system (CNS) and neurodevelopmental abnormalities could lead to an increased expression of NSS (Peralta et al., 2011). At the same time, schizophrenic psychoses are regarded as arising partly from neurodevelopmental problems. So there might be a shared common etiology of NSS and schizophrenic psychoses. As an indication of that, delayed speech or walking in childhood are important risk factors not only for neurological soft signs (Peralta et al., 2011), but also for schizophrenic psychoses (Welham et al., 2009). Moreover, some studies found a relationship between a history of obstetric complications and neurological soft signs (Bersani et al., 2012; Peralta et al., 2006) in schizophrenia patients. However, this relationship remains controversial as some found a negative relationship in schizophrenia (Mrad et al., 2010) or first-episode psychosis (Boks et al., 2007).

Thus, although the etiology of NSS remains unclear (Chan et al., 2010), the high prevalence of NSS in patients suffering from schizophrenic psychoses as well as their association with obstetric complications and neurodevelopmental delay have led to the assumption that these neurological abnormalities are an expression of underlying neurodevelopmental disturbances (Leask et al., 2002; Peralta et al., 2011).

Growing evidence proposes that NSS tend to be stable over time, irrespective of whether psychopathological symptoms are observable (Chan et al., 2010; Neelam et al., 2011). Due to their association to the illness, their presence irrespective of the disease state, and their familial association, NSS have been proposed as possible endophenotypes for schizophrenia (i.e. trait-markers that are present independent of the manifestation of the disease) (Chan and Gottesman, 2008; Neelam et al., 2011).

Although some authors have suggested NSS as potential trait-marker for psychosis proneness (Barkus et al., 2006), to our knowledge no study has yet examined NSS in a group of clinical At-Risk Mental State individuals (ARMS), i.e. individuals with clinical symptoms of a putative prodromal state of psychosis. Hence, the main goal of this study was to compare the NSS frequency in ARMS individuals who later in fact made the transition to psychosis (ARMS-T) to that of a group of FEP. Supporting a neurodevelopmental model of NSS, we expected to observe no difference between these two groups. Our secondary goal was to test whether NSS predict the transition to psychosis by comparing individuals at-risk who made the transition to psychosis and those who did not (ARMS-T vs. ARMS-NT). Because NSS have been reported to be more prevalent in patients with schizophrenia compared to other psychiatric disorders and non-psychiatric controls (Cox and Ludwig, 1979; Jaafari et al., 2011), we hypothesized that NSS would be more severe in ARMS-T than in ARMS-NT.

2. Methods and materials

2.1 Setting and recruitment

All data analyzed in this study were collected within the prospective ***F***rüh***e***rkennung von ***Psy***chosen (***FePsy***) study, which aims to improve the early detection of psychosis. A more detailed description of the overall study design can be found elsewhere (Riecher-Rössler et al., 2007; Riecher-Rössler et al., 2009). All participants were recruited between March 2000 and November 2003 via the ***FePsy***-Clinic at the Psychiatric Outpatient Department of the University Hospital Basel, which was set up specifically to identify, assess, and treat individuals in the very early stages of developing psychosis. The study was approved by the ethics committee of the University of Basel and all participants provided written informed consent.

Screening was performed with the Basel Screening Instrument for Psychosis (BSIP) (Riecher-Rössler et al., 2008), which is based on the DSM-III-R prodromal symptoms (American Psychiatric Association, 1987) and other early signs and risk factors, such as social decline, drug abuse, previous psychiatric treatment or genetic risk. It also incorporates four psychosis items of the expanded version of the Brief Psychiatric Rating Scale (BPRS) (Lukoff et al., 1986; Ventura et al., 1993) for assessing (pre-) psychotic phenomena. Individuals were classified by the BSIP as being in an At-Risk Mental State (ARMS) for psychosis, having a first episode psychosis (FEP), or not being at risk for psychosis (usually having other psychiatric disorders).

ARMS individuals met one of the following inclusion criteria: i) psychotic symptoms below the transition cut-off ("attenuated" psychotic symptoms) during the past year; ii)

psychotic symptoms above the transition cut-off, but not lasting more than a week and resolving spontaneously; iii) first or second degree relative with psychotic disorder and at least two further risk factors according to the screening instrument (not necessarily including the presence of pre-psychotic symptoms); and iv) unspecific risk factors and indicators, such as prodromal symptoms and marked social decline. These criteria are in close correspondence to those of the PACE clinic (Yung et al., 2007) and have been shown to have a good inter-rater reliability and a high predictive validity (Riecher-Rössler et al., 2008).

FEP individuals met the transition criteria to psychosis according to Yung et al. (1998) corresponding to at least one of the following symptoms at least several times a week during more than 1 week: i) suspiciousness (Brief Psychiatric Rating Scale (BPRS) > 5); ii) unusual thought content (BPRS >5); iii) hallucinations (BPRS >4); iv) conceptual disorganization (BPRS >5) (Lukoff et al., 1986; Ventura et al., 1993).

Exclusion criteria for both ARMS and FEP individuals were age younger than 18 years, insufficient knowledge of German, IQ <70, previous episode of a schizophrenic psychosis, psychosis clearly due to organic reasons or substance abuse, and psychotic symptoms within a clearly diagnosed depression or borderline personality disorder.

All ARMS and FEP individuals included in the *FePsy* study underwent an extensive entry examination. In addition, ARMS individuals were followed-up at regular intervals in order to distinguish those who later developed frank psychosis (ARMS-T) from those who did not (ARMS-NT). During the first year of the follow-up, ARMS individuals were assessed for transition to psychosis monthly, during the second and third years three-monthly, and thereafter annually. Transition to psychosis was monitored by applying the transition criteria of Yung et al. (1998) described above.

2.2. NSS assessment

Neurological soft signs were assessed at study entry using the modified and shortened version of the Neurological Evaluation Scale (NES) originally developed by Heinrichs & Buchanan (1988). The shortened version of the NES (Sanders et al., 1998) includes only the 13 items which have been shown to have a sufficient frequency (on each of these items, at least 10% of patients have a non-zero rating) and a consistent inter-rater reliability (Sanders et al., 2005).

The NES measures four domains: sensory integration, motor coordination, sequencing of complex motor acts, and other soft signs. Each item is rated 0 (no NSS), 1 (mild) or 2 (severe). The assessment of NSS has been conducted by three psychiatrists trained and supervised by the same psychiatrist/ neurologist (double qualification).

2.3. Diagnoses

Psychiatric diagnoses were assessed at study entry using a modified German version of the structured clinical interview for DSM-IV disorders (SCID-I) (Wittchen et al., 1997). The German version of the SCID-I also allows the transformation of DSM-IV diagnoses into ICD-10 diagnoses, which we report in this study.

2.4. Assessment of psychopathology

General psychopathology and positive psychotic symptoms were assessed by the expanded version of the BPRS (Lukoff et al., 1986; Ventura et al., 1993). The positive symptom scale was based on the BPRS items suspiciousness, hallucinations, unusual thought content, and

conceptual disorganization. Negative symptoms were assessed by the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989).

2.5. Statistical methods

The general analytic approach serves the purpose to give a description of the NSS frequency in our three samples (ARMS-NT, ARMS-T and FEP). The SPSS software for Windows (SPSS version 19; SPSS, Chicago, Illinois) was used. When the necessary preconditions were met, univariate analyses of covariance (ANCOVA) with age and sex as covariates were performed; when not, we opted for the non-parametric alternatives Kruskal-Wallis Test (for ordinal variables) and Chi-square Test (for dichotomous variables). Because the NSS total score was strongly positively skewed we used the log-transformed NSS total score in parametric group comparisons (i.e. ANOVAs) To test whether NSS predict the transition to psychosis in ARMS individuals, we performed a logistic regression analysis in which transition vs. non-transition was the dependent variable and the four NSS subscale scores served as independent variables.

3. Results

NSS were assessed in 16 ARMS-T, 37 ARMS-NT, and 27 FEP individuals. Table 1 shows the demographic and clinical characteristics of the three patient groups. 44 of the ARMS individuals (86.3%) were included due to either attenuated psychotic, brief limited intermittent psychotic symptoms or both, one (2%) was included due to genetic risk in combination with unspecific risk factors only and six (11.8%) were included due to unspecific

risk factors only. There was no statistically significant difference in the frequencies of risk groups between ARMS-T and AMRS-NT. All ARMS individuals and 51.8% of the FEP were antipsychotic naïve.

Most individuals with an ARMS also met the criteria for other diagnoses. Table 2 illustrates the diagnostic distribution.

---------- Tables 1 and 2 about here----------

The percentage of individuals with at least one NSS was 49% in ARMS-NT, 31% in ARMS-T and 37% in FEP. Table 3 illustrates percentages of ARMS-NT, ARMS-T and FEP displaying at least one neurological soft sign (mild or severe) for each domain and p-values for differences between groups (Kruskal-Wallis-Test). We carried out univariate analyses of covariance with group as between-subjects factor, total NSS score (log transformed) as dependent variable and sex and age as covariates. The analyses revealed no significant differences in the NSS total score neither between ARMS-NT, ARMS-T and FEP ($F(2,80)=2.025$, $p=0.139$) nor between ARMS-T and FEP analysed alone ($F(1,43)=0.685$, $p=0.413$), nor ARMS total group (T + NT) against FEP group ($F(1,80)= 0.142$, $p=0.708$), nor when comparing ARMS-T against ARMS-NT ($F(1, 53)=3.867$, $p=0.055$). Sex ($p= 0.233$) and age ($p=0.125$) did not significantly differ between groups.

A logistic regression model that included ARMS-T vs. ARMS-NT as dependent variable and the four NES subscales as independent variables revealed that the four NES subscales were not predictive for developing psychosis neither alone nor in combination (model likelihood ratio test: $\chi = 6.55$, $df = 4$, $p = 0.164$).

Also when examining the four sub-scores separately using Kruskal-Wallis tests we found no significant differences between our three groups: sensory integration (p=0.515), motor coordination (p=1.000), sequencing of complex motor acts (p=0.241) and other (p=0.617).

---------- Table 3 about here ----------

Mann-Whitney U tests indicated that FEP patients with antipsychotic medication (n = 13) did not differ from those without antipsychotic medication (n = 14) with regard to NES total and subscale scores. Furthermore, the proportions of FEP patients with at least one NSS were highly similar across groups (36% in unmedicated FEP and 38% in medicated FEP). Consequently, including antipsychotic medication as a covariate in patient group comparisons on NES total and subscale scores did not change the above described results. To examine whether neurological soft signs are associated with clinical symptoms, we calculated Spearman correlations between NES total score and SANS total, BPRS positive symptoms, and BPRS total scores. The results revealed that NES total was not significantly correlated with any of these scales, neither in the total group, nor in the ARMS and FEP groups (see Table 4). Accordingly, including BPRS total, BPRS positive symptoms and SANS total and as covariates in the above described ANCOVA models did not change our results.

---------- Table 4 about here ----------

4. Discussion

To the best of our knowledge, this is the first assessment of NSS in a group of individuals with a clinical risk for developing psychosis. Our first aim was to compare NSS frequency in at-risk mental state individuals who later made the transition to psychosis (ARMS-T) to that observed in a group of FEP. Since improving the prediction of psychosis is of high clinical

relevance (Fusar-Poli et al., 2012), our secondary goal was to test whether NSS predicts the transition to psychosis by comparing individuals at-risk who later made the transition to psychosis and those who did not (ARMS-T vs. ARMS-NT). Assuming NSS to represent a measurable manifestation of neurodevelopmental disruption, we expected i) to find NSS already in ARMS-T in about the same frequency as in FEP and ii) to find more NSS in the group of at-risk individuals who later made the transition to psychosis than in the group of those who did not.

As expected, the analysis revealed no significant differences between individuals at-risk with later transition to psychosis and first episode psychosis patients, i.e. NSS seem to be prevalent already before frank transition to psychosis. This finding provides further support to the proposed neurodevelopmental model of NSS. That is, minor neurological impairments may be signs of deviant brain development present before the development of frank psychosis. They might represent a trait-marker of vulnerability for psychosis (Mayoral et al., 2012), but potentially also of vulnerability for other neurodevelopmental disorders. The fact that we found no significant difference in the frequency of NSS between ARMS who later made the transition to psychosis and those who did not, seems to speak for the latter interpretation. Surprisingly, we even observed a trend in the opposite direction ($p=0.055$), with ARMS-NT individuals displaying a slightly higher prevalence rate than ARMS-T. This finding not only suggests a low predictive value of NSS for a transition to psychosis, but also a low specificity of NSS: in fact, they have been reported not only in schizophrenia but also in other psychiatric conditions and are likely to be nonspecific indicators of neurodevelopmental abnormalities (Gurvits et al., 2000; Negash et al., 2004). Thus, the high prevalence of NSS in our sample of ARMS-NT might also be associated with the psychiatric comorbidity in our patients without transition to psychosis or with the at-risk mental state

for psychosis itself,which means that these syndromes and disorders might also be associated with neurodevelopmental abnormalities. The fact that, in our sample, *all* individuals diagnosed with disorders of development or disorders occurring during childhood (F8 and F9) also displayed NSS, provides further support for our hypothesis that NSS may be mainly present in patients with a strong neurodevelopmental etiopathogenic mechanism of their disorder. On the other hand, as schizophrenic psychoses are most probably an etiologically heterogeneous group of disorders, it is likely that some of these patients present no or less severe signs of neurodevelopmental abnormalities.

4.1. Limitations

A major limitation of this study is the small group sizes, which does not allow definite conclusions. On the other hand, this – to our knowledge – is the first study investigating NSS in patients prodromal for psychosis, which are difficult to recruit and to follow up. The advantage of our sample is that it was followed for a long period of time (up to 7 years or until transition).Therefore, our results are really based on “true” prodromal patients. Another limitation of our study is that we did not measure NSS in a matched control group of healthy subjects. Thus, we can only assume from the literature that the frequencies of NSS detected in our groups are higher than in the general population.

4.2. Conclusions

To better understand the biological processes behind NSS and their value as biomarker for psychosis proneness, additional studies with larger samples of clinical ARMS-T and -NT individuals correlating the NSS with other indicators of neurodevelopmental abnormalities are necessary.

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References

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders, 3rd, revised ed. American Psychiatric Press, Washington DC.

Andreasen, N.C., 1989. The scale for the assessment of negative symptoms (SANS): Conceptual and theoretic foundations. British Journal of Psychiatry 155, 49-52.

Barkus, E., Stirling, J., Hopkins, R., Lewis, S., 2006. The Presence of Neurological Soft Signs Along the Psychosis Proneness Continuum. Schizophrenia Bulletin 32, 573-577.

Bersani, G., Clemente, R., Gherardelli, S., Bersani, F.S., Manuali, G., 2012. Obstetric complications and neurological soft signs in male patients with schizophrenia. Acta Neuropsychiatr 24, 344-348.

Boks, M.P., Selten, J.P., Leask, S., Castelein, S., van den Bosch, R.J., 2007. Negative association between a history of obstetric complications and the number of neurological soft signs in first-episode schizophrenic disorder. Psychiatry Res 149, 273-277.

Bombin, I., Arango, C., Buchanan, R.W., 2005. Significance and Meaning of Neurological Signs in Schizophrenia: Two Decades Later. Schizophrenia Bulletin 31, 962-977.

Borgwardt, S.J., McGuire, P., Fusar-Poli, P., Radü, E.W., Riecher-Rössler, A., 2008. Anterior cingulate pathology in the prodromal stage of schizophrenia. Neuroimage 39, 553-554.

Chan, R., Gottesman, I., 2008. Neurological soft signs as candidate endophenotypes for schizophrenia: A shooting star or a Northern star? Neuroscience & Biobehavioral Reviews 32, 957-971.

Chan, R.C., Xu, T., Li, H.J., Zhao, Q., Liu, H.H., Wang, Y., Yan, C., Cao, X.Y., Wang, Y.N., Shi, Y.F., Dazzan, P., 2011. Neurological abnormalities and neurocognitive functions in healthy elder people: a structural equation modeling analysis. Behavioral and brain functions : BBF 7, 32.

Chan, R.C.K., Xu, T., Heinrichs, R.W., Yu, Y., Wang, Y., 2010. Neurological Soft Signs in Schizophrenia: A Meta-analysis. Schizophrenia Bulletin 36, 1089-1104.

Chen, E.Y.-H., Hui, C.L.-M., Chan, R.C.-K., Dunn, E.L.-W., Miao, M.Y.-K., Yeung, W.-S., Wong, C.-K., Chan, W.-F., Tang, W.-N., 2005. A 3-year prospective study of neurological soft signs in first-episode schizophrenia. Schizophrenia Research 75, 45-54.

Cox, S.M., Ludwig, A.M., 1979. Neurological soft signs and psychopathology: I. Findings in schizophrenia. Journal of Nervous and Mental Disease 167, 161-165.

Dazzan, P., Morgan, K.D., Chitnis, X., Suckling, J., Morgan, C., Fearon, P., McGuire, P.K., Jones, P.B., Leff, J., Murray, R.M., 2006. The Structural Brain Correlates of Neurological Soft Signs in Healthy Individuals. Cerebral Cortex 16, 1225-1231.

Dazzan, P., Morgan, K.D., Orr, K.G., Hutchinson, G., Chitnis, X., Suckling, J., Fearon, P., Salvo, J., McGuire, P.K., Mallett, R.M., Jones, P.B., Leff, J., Murray, R.M., 2004. The structural brain correlates of neurological soft signs in ÆSOP first-episode psychoses study. Brain 127, 143-153.

Dazzan, P., Murray, R., 2002. Neurological soft signs in first-episode psychosis: a systematic review. The British Journal of Psychiatry 181, s50-s57.

Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, S., Kempton, M.J., Valmaggia, L., Barale, F., Caverzasi, E., McGuire, P., 2012. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry 69, 220-229.

Gourion, D., Goldberger, C., Olie, J.P., Lôo, H., Krebs, M.O., 2004. Neurological and morphological anomalies and the genetic liability to schizophrenia: a composite phenotype. Schizophrenia Research 67, 23-31.

Gurvits, T.V., Gilbertson, M.W., Lasko, N.B., Tarhan, A.S., Simeon, D., Macklin, M.L., Orr, S.P., Pitman, R.K., 2000. Neurologic Soft Signs in Chronic Posttraumatic Stress Disorder. Archives of General Psychiatry 57, 181-186.

Heinrichs, D., Buchanan, R., 1988. Significance and meaning of neurological signs in schizophrenia. American Journal of Psychiatry 145, 11-18.

Jaafari, N., Baup, N., Bourdel, M., Olié, J., Rotge, J., Wassouf, I., Sharov, I., Millet, B., Krebs, M., 2011. Neurological Soft Signs in OCD Patients With Early Age at Onset, Versus Patients With

Schizophrenia and Healthy Subjects. Journal of Neuropsychiatry and Clinical Neurosciences 23, 409-416.

Janssen, J., Diaz-Caneja, A., Reig, S., Bombín, I., Mayoral, M., Parellada, M., Graell, M., Moreno, D., Zabala, A., Vazquez, V.G., Desco, M., Arango, C., 2009. Brain morphology and neurological soft signs in adolescents with first-episode psychosis. The British Journal of Psychiatry 195, 227-233.

King, D.J., Wilson, A., Cooper, S.J., Waddington, J.L., 1991. The clinical correlates of neurological soft signs in chronic schizophrenia. The British Journal of Psychiatry 158, 770-775.

Lawrie, S.M., Byrne, M., Miller, P., Hodges, A., Clafferty, R.A., Owens, D.G.C., Johnstone, E.C., 2001. Neurodevelopmental indices and the development of psychotic symptoms in subjects at high risk of schizophrenia. The British Journal of Psychiatry 178, 524-530.

Leask, S.J., Done, D.J., Crow, T.J., 2002. Adult psychosis, common childhood infections and neurological soft signs in a national birth cohort. The British Journal of Psychiatry 181, 387-392.

Lukoff, D., Liberman, R.P., Nuechterlein, K.H., 1986. Symptom monitoring in the rehabilitation of schizophrenic patients. Schizophr Bull 12, 578-602.

Mayoral, M., Bombín, I., Castro-Fornieles, J., González-Pinto, A., Otero, S., Parellada, M., Moreno, D., Baeza, I., Graell, M., Rapado, M., Arango, C., 2012. Longitudinal study of neurological soft signs in first-episode early-onset psychosis. Journal of Child Psychology and Psychiatry 3, 323-331.

Mechri, A., Gassab, L., Slama, H., Gaha, L., Saoud, M., Krebs, M.O., 2010. Neurological soft signs and schizotypal dimensions in unaffected siblings of patients with schizophrenia. Psychiatry Res 175, 22-26.

Mergl, R., Hegerl, U., 2005. Neurologische Soft Signs bei Patienten mit Zwangsstörung (Übersichtsreferat). [Neurological Soft Signs in Patients with Obsessive-Compulsive Disorder.]. Fortschritte der Neurologie, Psychiatrie 73, 504-516.

Mohr, F., Hubmann, W., Albus, M., Franz, U., Hecht, S., Scherer, J., Binder, J., Sobizack, N., 2003. Neurological soft signs and neuropsychological performance in patients with first episode schizophrenia. Psychiatry Research 121, 21-30.

Mrad, A., Mechri, A., Slama, H., Mokni, S., Letaief, M., Gha, L., 2010. Correlations between obstetric complications and neurological soft signs in Tunisian patients with schizophrenia. Psychiatry Clin Neurosci 64, 645-648.

Neelam, K., Garg, D., Marshall, M., 2011. A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia. BMC Psychiatry 11, 139.

Negash, A., Kebede, D., Alem, A., Melaku, Z., Deyessa, N., Shibire, T., Fekadu, A., Fekadu, D., Jacobsson, L., Kullgren, G., 2004. Neurological soft signs in bipolar I disorder patients. Journal of Affective Disorders 80, 221-230.

Peralta, V., Cuesta, M., Serrano, J., 2006. Obstetric complications and neurological abnormalities in neuroleptic-naive psychotic patients. European Archives of Psychiatry and Clinical Neuroscience 256, 407-413.

Peralta, V., de Jalón, E.G., Campos, M.S., Basterra, V., Sanchez-Torres, A., Cuesta, M.J., 2011. Risk factors, pre-morbid functioning and episode correlates of neurological soft signs in drug-naive patients with schizophrenia-spectrum disorders. Psychological Medicine 41, 1279-1289.

Riecher-Rössler, A., Aston, J., Ventura, J., Merlo, M., Borgwardt, S., Gschwandtner, U., Stieglitz, R.D., 2008. The Basel Screening Instrument for Psychosis (BSIP): development, structure, reliability and validity. Fortschritte der Neurologie-Psychiatrie 76, 207-216.

Riecher-Rössler, A., Gschwandtner, U., Aston, J., Borgwardt, S., Drewe, M., Fuhr, P., Pflüger, M., Radü, W., Schindler, C., Stieglitz, R.D., 2007. The Basel early-detection-of-psychosis (FEPSY)-study – design and preliminary results. Acta Psychiatrica Scandinavica 115, 114-125.

Riecher-Rössler, A., Pflueger, M., Aston, J., Borgwardt, S., Brewer, W., Gschwandtner, U., Stieglitz, R., 2009. Efficacy of using cognitive status in predicting psychosis: a 7-year follow-up. Biol Psychiatry 66, 1023-1030.

Rossi, A., De Cataldo, S., Di Michele, V., Manna, V., Ceccoli, S., Stratta, P., Casacchia, M., 1990. Neurological soft signs in schizophrenia. The British Journal of Psychiatry 157, 735-739.

Sanders, R.D., Allen, D.N., D. Forman, S., Tarpey, T., Keshavan, M.S., Goldstein, G., 2005. Confirmatory factor analysis of the Neurological Evaluation Scale in unmedicated schizophrenia. Psychiatry Research 133, 65-71.

Sanders, R.D., Forman, S.D., Pierri, J.N., Baker, R.W., Kelley, M.E., Van Kammen, D.P., Keshavan, M.S., 1998. Inter-rater reliability of the neurological examination in schizophrenia. Schizophrenia Research 29, 287-292.

Smieskova, R., Fusar-Poli, P., Allen, P., Bendfeldt, K., Stieglitz, R.D., Drewe, J., Radue, E.W., McGuire, P.K., Riecher-Rössler, A., Borgwardt, S.J., 2010. Neuroimaging predictors of transition to psychosis--A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews 34, 1207-1222.

Theleritis, C., Vitoratou, S., Smyrnis, N., Evdokimidis, I., Constantinidis, T., Stefanis, N.C., 2012. Neurological soft signs and psychometrically identified schizotypy in a sample of young conscripts. Psychiatry Res 198, 241-247.

Thomann, P.A., Wüstenberg, T., Santos, V.D., Bachmann, S., Essig, M., Schröder, J., 2009. Neurological soft signs and brain morphology in first-episode schizophrenia. Psychological Medicine 39, 371-379.

Ventura, J., Lukoff, D., Nuechterlein, K.H., Liberman, R.P., Green, M., Shaner, A., 1993. Training and quality assurance with the brief psychiatric rating scale: "The Drift Busters"; Appendix 1. The Brief Psychiatric Rating Scale (expanded version). International Journal of Methods in Psychiatric Research 3, 221-224.

Welham, J., Isohanni, M., Jones, P., McGrath, J., 2009. The antecedents of schizophrenia: a review of birth cohort studies. Schizophrenia Bulletin 35, 603-623.

Wittchen, H.U., Wunderlich, U., Gruschwitz, S., Zaudig, M., 1997. [SCID-I—Structured Clinical Interview for DSM-IV; modified German version]. Hogrefe, Göttingen.

Yung, A.R., McGorry, P.D., Francey, S.M., Nelson, B., Baker, K., Phillips, L.J., Berger, G., Amminger, G.P., 2007. PACE: a specialised service for young people at risk of psychotic disorders. Medical Journal of Australia 187, S43-46.

Yung, A.R., Phillips, L.J., McGorry, P.D., McFarlane, C.A., Francey, S., Harrigan, S., Patton, G.C., Jackson, H.J., 1998. Prediction of psychosis: A step towards indicated prevention of schizophrenia. British Journal of Psychiatry 172, 14-20.

Table 1: Demographic and clinical characteristics

	ARMS-NT (*n*=37)	ARMS-T (*n*=16)	FEP (*n*=27)	*p*-value
Gender:				0.233
Women	19 (51.4%)	5 (31.2%)	9 (33.3%)	
Men	18 (48.6%)	11 (68.8%)	18 (66.7%)	
Age	26.7 (9.95)	27.0 (7.28)	31.2 (8.51)	0.125
Years of education	10.6 (3.09)	10.8 (2.32)	10.5 (3.12)	0.934
BPRS total score	39.4 (8.53)	41.2 (9.93)	55.9 (15.1)	<0.001
BPRS Positive symptoms	7.03 (2.39)	8.12 (2.50)	14.0 (3.46)	<0.001
SANS total score	22.6 (17.9)	28.9 (18.5)	33.1 (16.7)	0.062

Continuous variables are presented as means with standard deviations in parentheses. ARMS-T = at risk mental state with later transition to psychosis; ARMS-NT = at risk mental state without later transition to psychosis; FEP = first episode of psychosis; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms

Table 2: Diagnoses of Patients with an At-risk Mental State*

ICD-10 diagnoses	ARMS-NT (*n* = 37)		ARMS-T (*n* = 16)		ARMS *with* vs. *without* NSS
	with NSS (*n* = 18) n (%)	*without* NSS (*n* = 19) n (%)	*with* NSS (*n* = 5) n (%)	*without* NSS (*n* = 11) n (%)	Pearson's Chi-Square Test
F1	3 (17%)	5 (26%)	0 (0%)	2 (20%)	p=0.343
F3	9 (50%)	9 (47%)	2 (40%)	4 (40%)	p=0.745
F4	2 (11%)	4 (21%)	0 (0%)	1 (10%)	p=0.396
F8 and F9	2 (11%)	0 (0%)	1 (20%)	0 (0%)	p=0.042

*Diagnoses based on ICD-10 (International Classification of Diseases) in addition to "At Risk Mental State"
ARMS-T = at risk mental state with later transition to psychosis; ARMS-NT = at risk mental state without later transition to psychosis; NSS = neurological soft signs

F1: Mental and behavioural disorders due to psychoactive substance use
F3: Mood [affective] disorders
F4: Neurotic, stress-related and somatoform disorders
F8: Disorders of psychological development
F9: Behavioural and emotional disorders with onset usually occurring in childhood and adolescence

Table 3: Percentage of ARMS-NT, ARMS-T and FE Displaying At Least One Neurological Soft Sign

	ARMS-NT	ARMS-T	FE	ARMS-T vs. ARMS-NT vs. FE	ARMS-T vs. FE	ARMS-T vs. ARMS-NT
Sensory integration	27%	12%	26%	p=0.515	p=0.668	p=0.668
Motor coordination	3%	0%	4%	p=1.00	p=1.00	p=1.00
Sequencing of complex motor acts	28%	6%	22%	p=0.241	p=0.344	p=0.344
Other	16%	12%	8%	p=0.617	p=0.943	p=1.00
NSS pathology (total)	49%	31%	37%	p=0.429	p=0.957	p=0.755

ARMS-T = at risk mental state with later transition to psychosis; ARMS-NT = at risk mental state without later transition to psychosis; FE = first episode of psychosis; NSS = neurological soft signs

Neurological soft signs (mild or severe) for each domain and overall
P-values for differences between groups with regard to sum scores (Kruskal-Wallis-Test)

Table 4: Spearman correlations between NES total and clinical symptoms

Patient group	Scale	*n*	Correlation coefficient (rho)	*p*-value
Total group	BPRS Positive Symptoms	80	-0.09	0.415
Total group	BPRS total	80	-0.12	0.271
Total group	SANS total	80	0.11	0.343
ARMS	BPRS Positive Symptoms	53	-0.11	0.451
ARMS	BPRS total	53	-0.14	0.312
ARMS	SANS total	53	0.16	0.256
FEP	BPRS Positive Symptoms	27	0.05	0.817
FEP	BPRS total	27	-0.10	0.636
FEP	SANS total	27	-0.11	0.577

NES = Neurological Evaluation Scale; ARMS = at risk mental state; FEP = first episode of psychosis; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms