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

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ABSTRACT

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. 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*. 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. 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.

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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 volumes 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 and frontal gyrus), independent of antipsychotic medication (Dazzan et al., 2004; Janssen et al., 2009; Thomann et al., 2009). These regions,

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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 other studies 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; Chen et al., 2005). 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 (ARMS) individuals, 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 with 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*rüherkennung von *Ps*ychosen (*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, 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 for more than 1 week: (i) suspiciousness (Brief Psychiatric Rating Scale (BPRS) >5); (ii) unusual thought content (BPRS >5); (iii) hallucinations (BPRS >4); and (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.

In all ARMS and FEP individuals included in the *FePsy* study underwent an extensive entry examination was performed. 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) as 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 and 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 the 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, IL) was used. When the

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