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Motor dysfunction as research domain in the period preceding manifest schizophrenia: A systematic review

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ABSTRACT

Schizophrenia is a severe behavioral syndrome of neurodevelopmental nature marked by primary or genuine motor abnormalities (GMA), which refer to spontaneous and medication-independent motor phenomena. Since motor dysfunction thus might be a consequence of events occurring during early childhood and adolescence, GMA can be detected in the period preceding manifest schizophrenia. However, the question whether motor system dysfunction might be a promising motor intermediate phenotype for schizophrenia remains unanswered. In this review, we systematically evaluate the evidence on GMA in healthy persons, individuals with schizotypal personality traits, persons at ultra-high risk for psychosis, and unaffected first-degree relatives of schizophrenia patients. What becomes evident is a continuum of GMA expression, which appears to be linked to abnormalities of cerebello-thalamo-cortical, fronto-parietal, and cortico-subcortical motor circuits. According to current evidence, motor dysfunction is a key aspect of the neurodevelopmental risk factor model of schizophrenia. Insights provided by this research will help promoting the RDoC Motor System construct and expand the clinical relevance of the motor domain in the period preceding manifest schizophrenia.

1. Introduction

The recognition of motor dysfunction as an intrinsic feature of schizophrenia and related spectrum-disorders is long-standing (Peralta et al., 2010; Peralta and Cuesta, 2001b,2001a). However, after the introduction of antipsychotic drugs in the 1950s, motor symptoms and signs in schizophrenia have been lumped together with extrapyramidal side-effects of antipsychotic medication and lost their clinical and academic relevance. It was not until mid-1980s that clinical investigations in antipsychotic-naive first-episode schizophrenia patients found highly significant rates of movement abnormalities (Peralta et al., 2014). These studies suggested that motor symptoms may not only be drug-induced, but also genuine and intricately linked to the psychotic disorder itself (Morrens et al., 2014; Walther and Strik, 2012; Hirjak et al., 2015b). The term primary or *"genuine motor abnormalities"* (GMA) refers to spontaneous and medication-independent motor phenomena, which occur approximately in 80% of schizophrenia patients (Walther and Strik, 2012; Hirjak et al., 2015b,2015c). GMA comprise a broad spectrum of motor signs and symptoms and can be categorized into four groups: (1) neurological soft signs (NSS), (2) hyperkinetic abnormal involuntary movements (AIMS) such as dyskinesia, dystonia, akathisia or hyperkinesia, (3) hypokinetic AIMS such as spontaneous Parkinsonism, and (4) catatonic phenomena. Catatonia can present as hyperkinetic (mannerisms, stereotypy, excitement, perseveration, etc.) or hypokinetic (catalepsy, stupor, rigidity, immobility, mutism, etc) movement disorder. However, there is still a lack of consensus on the definition of abnormal motor behavior and delineation of particular motor symptoms in schizophrenia. Therefore, individual GMA categories should be viewed together within the context of a *"motor dimension"* (Hirjak et al., 2015b). Recent evidence supports this view and suggests that GMA gradually intensifies within a continuum ranging from healthy persons exhibiting low NSS scores, to persons at ultra-high risk (UHR) for psychosis and schizotypal individuals experiencing moderate NSS or subtle AIMS, to unaffected first-degree relatives of schizophrenia patients experiencing various degrees of NSS and AIMS, and finally to schizophrenia patients presenting with severe AIMS or catatonic symptoms (Hirjak et al., 2015b; Dazzan and Murray, 2002).

To date, the majority of findings on GMA stems from studies on NSS in schizophrenia patients (see the meta-analysis by Zhao et al. (Zhao et al., 2014) and reviews by Hirjak et al. (Hirjak et al., 2015b,2015c) for

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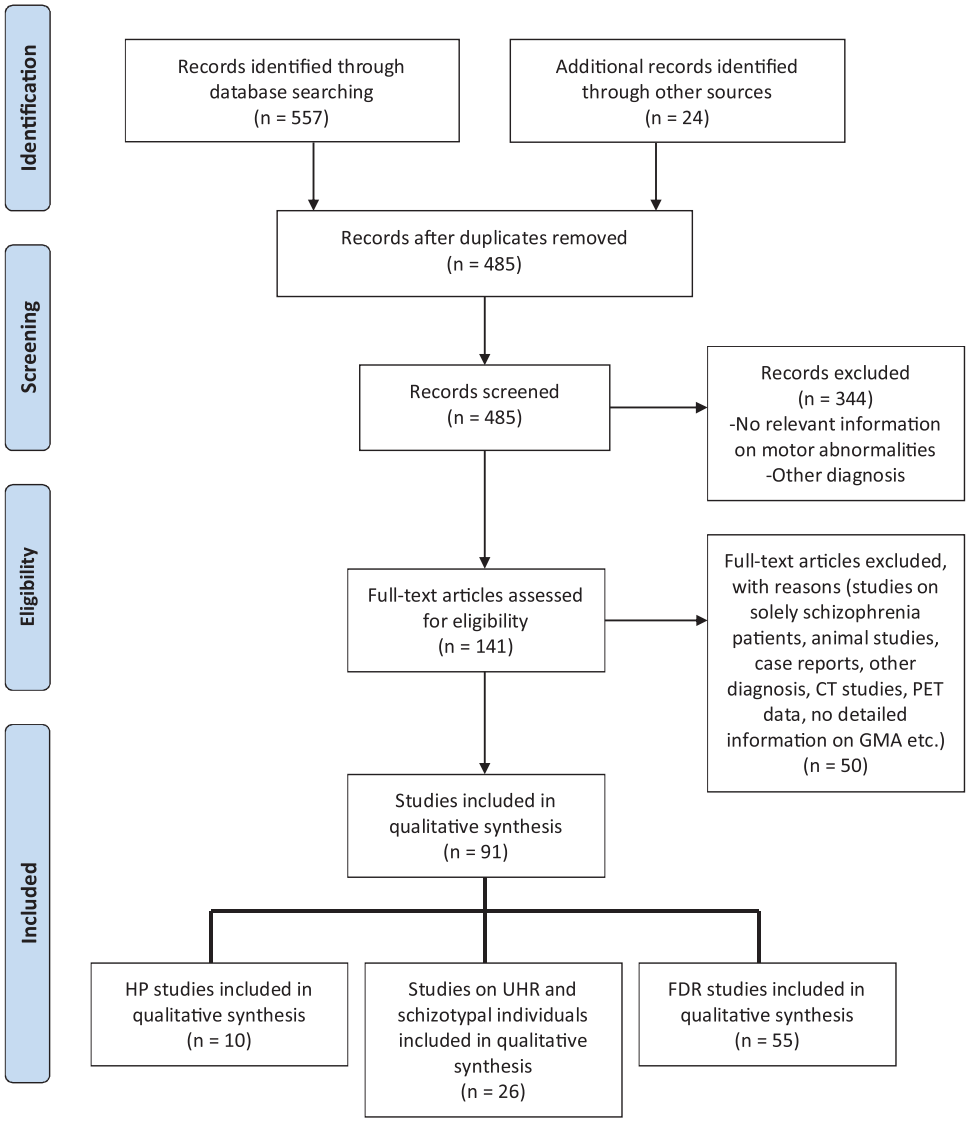

Fig. 1. PRISMA flow chart of included studies on genuine motor abnormalities in healthy persons, ultra-high risk individuals, individuals with schizotypal traits and unaffected first-degree relatives of schizophrenia patients.

further details). Recent neuroimaging studies investigating the neural underpinnings of GMA in schizophrenia patients have revealed structural and functional alterations in cortical and subcortical brain areas (for review see (Hirjak et al., 2015b; Walther and Strik, 2012)). These studies strongly support the hypothesis that GMA are linked to a disrupted cortico-cerebellar-thalamic-cortical circuit (Andreasen et al., 1998; Wiser et al., 1998). However, antipsychotic medication, duration of illness, comorbid diagnoses, heterogeneous clinical rating instruments, and the variability of psychopathological symptoms in manifest schizophrenia may hamper the search for neurobiological substrates of GMA.

Given that schizophrenia is characterized by high heritability and having an affected first-degree relative significantly increases the risk for later development of schizophrenia, there is a strong gene-brain and brain-symptom interaction in this disorder (Allen et al., 2009; Tost et al., 2010; Cao et al., 2016). However, clinical heterogeneity within schizophrenia makes the search for underpinning mechanisms and susceptibility genes candidates even more difficult. This effort may benefit from an intermediate phenotype approach, assuming neurobiological traits that are quantitative in nature, heritable, reliably measurable, associated with the illness in the general population, linked to genetic risk for schizophrenia, and state independent (Cao et al., 2016; Meyer-Lindenberg and Weinberger, 2006; Honea et al., 2008). According to recent neuroimaging and electrophysiological studies, several disease-related intermediate phenotypes in schizophrenia and their unaffected first-degree relatives (Allen et al., 2009) have been proposed such as ventricular, planum temporale and superior temporal gyrus volume, as well as aberrant neural activity in anterior cingulate and dorsolateral prefrontal cortex dysfunction, P50-ratio, or P300-response (Allen et al., 2009). Motor dysfunction, as illustrated by GMA-associated neural correlates appears to be less phenotypically complex and objectively more measurable than schizophrenia symptoms such as delusions, hallucinations or formal thought disorder. Therefore, neural correlates of NSS, AIMS, and catatonic symptoms can beneficially highlight the concept of biological intermediacy in pathogenesis of schizophrenia and serve as neuroimaging intermediate phenotype (Hirjak et al., 2017a). However, it is still not clear whether motor system dysfunction is genetically mediated by susceptibility gene candidates for schizophrenia and traceable in carriers of genetic risk variants. A promising strategy to answer these preeminent questions is the investigation of individuals with psychosis proneness and persons in the period preceding manifest schizophrenia. The following groups of persons seem to be most suitable for this purpose: (1) healthy persons exhibiting subtle GMA, (2) individuals with schizotypal personality