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Motor dysfunction as an intermediate phenotype across schizophrenia and other psychotic disorders: Progress and perspectives

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ABSTRACT

Primary motor abnormalities (PMA), as found in patients with schizophrenia, are quantitatively and qualitatively distinct markers of motor system abnormalities. PMA have been often referred to phenomena that are present across schizophrenia-spectrum disorders. A dysfunction of frontoparietal and subcortical networks has been proposed as core pathophysiological mechanism underlying the expression of PMA. However, it is unclear at present if such mechanisms are a common within schizophrenia and other psychotic disorders. To address this question, we review recent neuroimaging studies investigating the neural substrates of PMA in schizophrenia and so-called "*nonschizophrenic nonaffective psychoses*" (NSNAP) such as schizophreniform, schizoaffective, brief psychotic, and other unspecified psychotic disorders. Although the extant data in patients with schizophrenia suggests that further investigation is warranted, MRI findings in NSNAP are less persuasive. It is unclear so far which PMA, if any, are characteristic features of NSNAP or, possibly even specific for these disorders. Preliminary data suggest a relationship between relapsing-remitting PMA in hyper-/hypokinetic cycloid syndromes and neurodegenerative disorders of the basal ganglia, likely reflecting the transnosological relevance of subcortical abnormalities. Despite this evidence, neural substrates and mechanisms underlying PMA that are common in schizophrenia and NSNAP cannot be clearly delineated at this stage of research. PMA and their underlying brain circuits could be promising intermediate phenotype candidates for psychotic disorders, but future multimodal neuroimaging studies in schizophrenia and NSNAP patients and their unaffected first-degree relatives are needed to answer fundamental transnosologic questions.

1. Introduction

The first mention of motor dysfunction as an intrinsic feature of schizophrenia can be traced earlier than the beginning of twentieth century (Compton et al., 2015; Fink, 2013; Kahlbaum, 1874). In his textbook "*Die Katatonie oder das Spannungsirresein*" (Kahlbaum, 1874), Kahlbaum labeled a specific motor syndrome in psychotic patients as *catatonia* (Fink, 2013; Fink et al., 2010; Kahlbaum, 2007; Rogers, 1991). The earliest twentieth century scientific mentions of motor symptoms in schizophrenia can been attributed to Bleuler (1911) and Kreapelin (1899), who classified catatonia as one aspect of dementia praecox (Heckers, 2011; Peralta and Cuesta, 2011). However, with the first clinical description of drug-induced akathisia (Sigwald et al., 1947) and tardive dyskinesia (Schonecker, 1957) the majority of motor abnormalities in schizophrenia were classified as side-effects of antipsychotic drug treatment. By the 1960s, motor symptoms in schizophrenia were firmly established as drug-induced, albeit of unclear neurobiological pathogenesis. It was only in the mid-1980s that researchers begun to focus on motor abnormalities in antipsychotic-naïve schizophrenia patients. In line with previous observations in the "*pre-antipsychotic era*", significant rates of motor symptoms were observed, suggesting that motor dysfunction may not be drug-induced, but rather primary and intricately linked to schizophrenia itself (Compton et al., 2015; Friedman, 2004; Peralta et al., 2010; Peralta and Cuesta, 2001a). It is worth noting that in terms of what "*primary*" motor abnormalities actually are, there has been a historic tension between competing views of how "*primary*" motor symptoms should be defined, i.e. in which respect they may be primary or secondary to a specific disorder or medical condition. In accordance with other researchers (Francis et al., 2010; Jahn, 1999, 2004a, 2004b, 2005; Jahn et al., 2006a; Jahn et al., 2006b), our understanding of "*primary*" motor phenomena carries the explicit assumption that the etiology of these conditions is based on the mental disorder itself.

In clinical practice, primary motor abnormalities (PMA) superficially resemble neuroleptic-induced motor symptoms (e.g. Parkinsonism,

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tardive dyskinesia, dystonia, and tremor), but are not associated with antipsychotic use. Although different labels have been used to describe PMA, the specific demarcation between PMA and antipsychotic-induced motor symptoms requires substantial clinical experience. From a clinical perspective, spontaneous motor behavior in schizophrenia includes both decreased (e.g. psychomotor retardation, poverty of movement, stupor, motor blocking, last minute responses, and ambitendency) and increased activity (restlessness, excitement, tremor, agitation, motor impulsiveness, tics, choreiform movements, etc.) (Manschreck, 1993). Furthermore, schizophrenia patients are also characterized by postural disturbances such as rigidity, catalepsy, stereotypic/manneristic postures, and clumsiness (Manschreck, 1993). In contrast, drug-related motor effects comprise acute dystonias, akathisia (subjective motor restlessness), slowing, reduced spontaneity, immobile facies, reduced gait-associated movements, and tardive dyskinesia (Manschreck, 1993). While between 1960s and 1990s, psychiatric research about motor symptoms in schizophrenia has focused almost entirely on drug-induced dyskinesia, in the last two decades it became clear that research on both groups of motor abnormalities is of great practical importance.

Correspondingly, three distinct types of PMA have been systematically described in patients with schizophrenia: (1) neurological soft signs (NSS), (2) hyper-/hypokinetic abnormal involuntary movements (AIMS), and (3) catatonic phenomena (Compton et al., 2015; Cummings and Wirshing, 1992; Northoff et al., 1999a; Northoff et al., 2004). NSS comprise discrete impairments in motor coordination, sensory integration, balance, and sequencing of complex motor acts (Cummings and Wirshing, 1992; Schroder et al., 1991). Spontaneous or non-drug-induced AIMS are characterized by both hyper- and hypokinetic motor abnormalities such as dyskinesia, repetitive and involuntary choreiform movements, akathisia, hyperkinesia, dystonia, and spontaneous Parkinsonism (SP), respectively (Compton et al., 2015; Peralta et al., 2014; Walther and Strik, 2012). Catatonic phenomena comprise more than 40 affective, behavioral and motor symptoms (e.g. stupor, mutism, waxy flexibility, rigidity, posturing, mannerism, negativism, and stereotypy) (Fink and Taylor, 2009; Francis et al., 2010; Northoff, 2002; Walther and Strik, 2012).

PMA have been frequently discussed as features that may specifically apply to psychotic disorders, and particularly to schizophrenia (Abboud et al., 2017; Bernard and Mittal, 2015; Walther and Strik, 2012). It is unclear so far, whether PMA are characteristic for the entire psychosis spectrum, i.e. schizophreniform disorder, schizoaffective disorder, brief psychotic disorders, and other unspecified psychotic disorders. At first glance, this assumption may be valid assuming a dimensional model of symptom expression within the disease spectrum. Yet the vast majority of the studies on PMA have been performed in patients suffering from schizophrenia, and few studies included mixed psychotic populations including schizoaffective or schizophreniform disorders (Heuser et al., 2011; Stegmayer et al., 2014; Thomann et al., 2009b; Walther, 2015). So far, little is known to what extent these findings are valid across the entire disease spectrum. i.e. whether common or distinct biological mechanisms underlying PMA regardless of disorder category. Therefore, the major purpose of this paper was to fill these gaps in knowledge drawing on data from neuroimaging studies investigating the neural substrates of PMA in schizophrenia and related psychotic disorders. We will first define significant structural and functional neural circuits underlying PMA in schizophrenia. Next, structural and functional findings from schizophreniform, schizoaffective, brief psychotic disorders, and other unspecified psychotic disorders (e.g. delusional disorder) will be addressed. This group of relapsing-remitting disorders or so-called "*non-schizophrenic nonaffective psychoses*" (NSNAP) has been historically acknowledged as "*motility psychoses*" (Peralta and Cuesta, 2017), due to their polymorph psychotic symptom expression with rapid symptom change, mostly benign outcome, and (clinically frequently leading symptoms) abnormal psychomotor behavior (Pfuhlmann, 1998; Pfuhlmann et al., 1998). In this context, we propose that NSNAP patients exhibit very variable spontaneous motor behavior mainly in terms of decreased and increased activity associated with distinct motor networks. Eventually, such episodic motor behavior is subsequent to affective fluctuations itself.

We hypothesize that brain regions underlying PMA in NSNAP might be associated with both motor and affective neural networks. Given that there is preliminary evidence for the presence of PMA in unaffected first-degree relatives of schizophrenia patients (Chan et al., 2010a; Koning et al., 2010), this review seeks to evaluate current evidence for a putative "*intermediate motor phenotype*" in NSNAP, in terms of behavior, brain structure and brain function. Finally, we briefly summarize both progress and challenges for scientists that seek to overcome methodological constraints when investigating PMA in psychotic disorders.

2. Neuroimaging of neuronal circuits of PMA

2.1. Schizophrenia

The extant knowledge on putative pathomechanisms of PMA in psychotic disorders comes from behavioral and neuroimaging studies in schizophrenia (Khot and Wyatt, 1991; Mittal and Walker, 2009; Chan et al., 2010b). On one side, these studies demonstrated that NSS are related to morphological alterations within subcortical structures such as caudate nucleus (Dazzan et al., 2004; Hirjak et al., 2012; Janssen et al., 2009; Thomann et al., 2009b), putamen (Dazzan et al., 2004; Kasparek et al., 2009; Venkatasubramanian et al., 2008), globus pallidus (Dazzan et al., 2004; Hirjak et al., 2012), thalamus (Dazzan et al., 2004; Janssen et al., 2009; Thomann et al., 2009b), cerebellum (Bottmer et al., 2005; Hirjak et al., 2015b; Mouchet-Mages et al., 2007; Thomann et al., 2009a; Venkatasubramanian et al., 2008), and brainstem (Hirjak et al., 2013), respectively. On the other side, the above-mentioned studies pointed to NSS-related morphological alterations in the primary motor cortex (M1) and postcentral gyrus, premotor area, temporal and lingual gyri, middle and inferior frontal gyri, inferior parietal lobule, insula, precuneus and occipital gyrus, respectively (Hirjak et al., 2014; Zhao et al., 2014). This evidence has also been supported by a recent activation likelihood estimation (ALE) meta-analysis (Zhao et al., 2014). However, the question regarding the long-term course of NSS-related brain changes in schizophrenia still remains unclear, because there is only one longitudinal MRI study on NSS in schizophrenia available (Kong et al., 2015). Kong and colleagues (Kong et al., 2015) found NSS to be associated with cortical thinning in the prefrontal, inferior temporal, superior parietal, postcentral, and supramarginal areas. Considering white matter, NSS severity has been previously associated with the internal capsule, the medial and inferior frontal gyri, the corpus callosum, the precuneus, the corticospinal tract (Huttlova et al., 2014), and the superior cerebellar peduncle (Huttlova et al., 2014) (Bersani et al., 2011; Dazzan et al., 2004; Heuser et al., 2011; Mouchet-Mages et al., 2011; Thomann et al., 2009b).

Functional MRI studies found abnormal BOLD responses in pre- and postcentral gyri, premotor area, and middle and inferior frontal gyri as critical regions associated with NSS (Kodama et al., 2001; Muller et al., 2002; Rogowska et al., 2004; Schroder et al., 1999; Schroder et al., 1995). Driven by task-based functional neuroimaging data, recent ALE meta-analysis revealed that NSS were linked to altered task-related activation in the inferior frontal gyrus, bilateral putamen, the cerebellum and the superior temporal gyrus (Zhao et al., 2014). Regarding morphological brain alterations underlying NSS in unaffected FDR of SSD patients, we identified only one MRI study that directly compared NSS-related brain morphology in FDR and first-episode SSD patients. Chan and colleagues (Chan et al., 2015) examined 13 patients with first-episode schizophrenia, 14 non-psychotic FDR and 14 HP. The authors concluded that the NSS-related activity changes of the left frontoparietal might be a potential endophenotype of SSD. This might contribute to partly explain which regions are relevant for the development of NSS in FDR. Such research may facilitate explicit hypothesis testing when

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