Psychiatry Research: Neuroimaging 233 (2015) 293–298

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Review article

Psychomotor symptoms of schizophrenia map on the cerebral motor circuit ☆

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ARTICLE INFO

Article history:
Received 13 September 2014
Received in revised form
13 November 2014
Accepted 24 June 2015

Keywords:
Motor system
Diffusion tensor imaging (DTI)
Arterial spin labeling (ASL)
Functional magnetic resonance imaging (fMRI)

ABSTRACT

Schizophrenia is a devastating disorder thought to result mainly from cerebral pathology. Neuroimaging studies have provided a wealth of findings of brain dysfunction in schizophrenia. However, we are still far from understanding how particular symptoms can result from aberrant brain function. In this context, the high prevalence of motor symptoms in schizophrenia such as catatonia, neurological soft signs, parkinsonism, and abnormal involuntary movements is of particular interest. Here, the neuroimaging correlates of these motor symptoms are reviewed. For all investigated motor symptoms, neural correlates were found within the cerebral motor system. However, only a limited set of results exists for hypokinesia and neurological soft signs, while catatonia, abnormal involuntary movements and parkinsonian signs still remain understudied with neuroimaging methods. Soft signs have been associated with altered brain structure and function in cortical premotor and motor areas as well as cerebellum and thalamus. Hypokinesia is suggested to result from insufficient interaction of thalamocortical loops within the motor system. Future studies are needed to address the neural correlates of motor abnormalities in prodromal states, changes during the course of the illness, and the specific pathophysiology of catatonia, dyskinesia and parkinsonism in schizophrenia.

Contents

1. Introduction

Schizophrenia is a devastating disorder with suspected neurodevelopmental origins and a lifetime trajectory. The first symptoms usually occur during adolescence and early adulthood. The

☆Paper read in the Symposium of the 25th anniversary of the Internal Society of Neuroimaging in Psychiatry, Geneva September 2013.

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http://dx.doi.org/10.1016/j.pscychresns.2015.06.010
0925-4927/

syndrome includes various symptom dimensions including delusions, hallucinations, disorganized speech and aberrant motor behavior (Tandon et al., 2009; Heckers et al., 2013). Since schizophrenia is regarded as a brain disease, neuroscience has put much effort trying to unravel the neural basis of schizophrenia. From the early neuropathological investigations to more than four decades of ever advancing neuroimaging studies, a wealth of scientific articles on cerebral correlates of schizophrenia have been gathered. Still, the knowledge on the cerebral pathobiology of schizophrenia appears disappointingly limited and often contradictory. Some hypotheses and key findings survived over years and have been corroborated with different imaging methods, e.g., hypofrontality (Buchsbaum et al., 1982) or schizophrenia as a syndrome of cerebral disconnectivity (Clark et al., 1984) and later reviewed by others (Weinberger and Berman, 1996; Friston, 1999).

These general findings in patients with schizophrenia provide little evidence on exactly how symptoms in schizophrenia are elicited. Again, since schizophrenia is considered a brain disease, we need to explain how – under specific circumstances – one brain would produce a particular set of schizophrenia symptoms while the brain of another person would elicit different symptoms or no symptoms at all. Most imaging findings of cerebral alterations in groups of patients with schizophrenia fail to provide specific information on how the reported abnormalities contribute to the clinical presentation or pathological behavior.

A particular problem in neuroscientific research is the vast heterogeneity in clinical presentation, i.e., the diagnosis may apply to patients with completely distinct symptom profiles or symptom trajectories (Andreasen, 1999; Insel, 2010). Therefore, attempts to map symptoms to specific aberrant brain function have been frustrating when a study included all subjects who qualify for the schizophrenia diagnosis. An alternative approach is to investigate neural correlates of specific symptoms in groups of patients who suffer from these particular problems (Strik and Dierks, 2011). This symptom-catching approach to schizophrenia neuroimaging has been successful in research on auditory verbal hallucinations (Kindler et al., 2013), formal thought disorders (Horn et al., 2009, 2010), emotional dysregulation (Stegmayer et al., 2014b), and motor signs (Walther et al., 2011a, 2011b; Stegmayer et al., 2014a). The present selective review will provide an overview of representative studies particularly focusing on motor symptoms that have been mapped on the cerebral motor system in schizophrenia. Furthermore, we will discuss the outlook of research in this field.

2. Structural alterations in the motor system

The basic model of the human cerebral motor system is depicted in the figure (left part). The alterations of brain structure frequently reported in schizophrenia extend to both gray and white matter. Aberrant brain structures associated with schizophrenia are spread widely through the motor system of the brain, and are found in the frontal and temporal lobes as well as the basal ganglia and thalamus (Haijma et al., 2013). In fact, gray matter reductions have been found in the anterior cingulate cortex (ACC), the supplementary motor area (SMA), the pre-SMA, the primary motor cortex, the ventral premotor cortex (vPMC), the thalamus and the cerebellum. For the caudate nucleus and pallidum, findings have been inconsistent with studies reporting increased (Gur et al., 1998), unchanged (Glenthoj et al., 2007) and decreased volumes in schizophrenia (Ballmaier et al., 2008). Most of these gray matter alterations have been corroborated in meta-analyses (Ellison-Wright et al., 2008; Bora et al., 2011; Haijma et al., 2013). Diffusion tensor imaging (DTI) studies demonstrated aberrant white matter ultrastructure in some of the major fiber tracts containing motor pathways, such as the corpus callosum, corticospinal tract and internal capsule in schizophrenia (Walther and Strik, 2012). Thus, subtle aberrant brain connectivity within the cerebral motor system is a common finding in schizophrenia patients.

3. Motor dimension and types of symptoms

Motor symptoms frequently observed in schizophrenia are (1) abnormal involuntary movements (also termed dyskinesia); (2) neurological soft signs (NSS) referring to motor coordination, sequencing and sensory integration; (3) catatonic symptoms including pure motor signs, disturbance of volition, inability to suppress motor reactions and vegetative instability; (4) parkinsonism; and (5) psychomotor slowing, e.g., slowness in planning and execution of fine motor tasks and general hypokinesia (Walther and Strik, 2012). The motor symptoms are prevalent in both medicated and unmedicated patients, from the first episode throughout the course of the disorder (Wolff and O'Driscoll, 1999; Peralta and Cuesta, 2001, 2010; Docx et al., 2012; Walther and Strik, 2012). Dyskinesia, parkinsonism and neurological soft signs are also present in unaffected first degree relatives of patients or in subjects at risk for developing psychosis (Whitty et al., 2009; Walther and Strik, 2012). This indicates that motor symptoms represent an intrinsic part of schizophrenia pathobiology.

4. Neuroimaging of motor symptoms

In general, the clinical motor symptoms relate to different steps in the generation of motor action and will therefore map on both segregated and overlapping modules of the cerebral motor system.

4.1. Abnormal involuntary movements

Abnormal involuntary movements are hyperkinetic movement disorders caused by excessive involuntary muscle activity. Typically, the choreatiform movements consist of irregular fragments of normal movement but critically disturb motor control. These movements are thought to stem from abnormal striatopallidal activity, which finally leads to disinhibition of the thalamocortical projections (Obeso et al., 2014). Abnormal involuntary movements are frequently located in the distal extremities and orofacial regions in schizophrenia (Whitty et al., 2009; Walther and Strik, 2012).

In schizophrenia modern neuroimaging studies on tardive dyskinesia have revealed alterations of both gray and white matter properties. Gray matter was reduced in patients with dyskinesia compared with patients without dyskinesia in the inferior frontal gyrus bilaterally and in the right superior frontal gyrus. This reduction in volume was correlated with dyskinesia severity (Li et al., 2013). Likewise, a DTI study in patients with schizophrenia and tardive dyskinesia reported lower fractional anisotropy (FA) in white matter surrounding the inferior frontal gyrus, the basal ganglia, the dorsolateral prefrontal cortex, and the somatosensory cortex. Dyskinesia severity was correlated with reduced FA values in these regions (Bai et al., 2009). Results of earlier studies on cerebral correlates of dyskinesia with manual segmentation methods were inconclusive (for review, see Walther and Strik, 2012). Interestingly, spontaneous abnormal involuntary movements (detected prior to antipsychotic exposure) as measured by force instability were found to be associated with smaller bilateral putamen volumes in subjects at risk for psychosis (Mittal et al., 2013).