

Review

Brain connectivity in psychiatric imaging genetics

Heike Tost, Edda Bilek, Andreas Meyer-Lindenberg*

Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

ARTICLE INFO

Article history:

Received 15 July 2011

Revised 2 November 2011

Accepted 2 November 2011

Available online 9 November 2011

Keywords:

Connectivity

Imaging genetics

Psychiatric disorders

Neural networks

ABSTRACT

In the past decade, imaging genetics has evolved into a highly successful neuroimaging discipline with a variety of sophisticated research tools. To date, several neural systems mechanisms have been identified that mediate genetic risk for mental disorders linked to common candidate and genome-wide-supported variants. In particular, the examination of intermediate connectivity phenotypes has recently gained increasing popularity. This paper gives an overview of the scientific methods and evidence that link indices of neural network organization to the genetic susceptibility for mental illness with a focus on the effects of candidate genes and genome-wide supported risk variants on brain structure and function.

© 2011 Elsevier Inc. All rights reserved.

Contents

Introduction	2250
Imaging genetics: principles, challenges, and historical milestones	2251
Principles and challenges	2251
Candidate and genome-wide approaches	2252
Gene effects on functional network interaction	2252
Gene effects on structural network composition	2253
Structural covariance	2254
Diffusion imaging	2256
Gene effects on network topology	2256
Limitations	2257
Future directions	2258
References	2258

Introduction

One hundred years ago, at the cradle of modern neuroscience, the cytoarchitectonic definition of 48 distinct cortical regions by Korbinian Brodmann (1868–1918) provided a first glimpse of the complexity of cortical architecture (Brodmann, 1909), but the underlying biological principles of regional organization remained elusive. To date, after decades of substantial progress in neuroscience, the human brain is conceptualized as a complex network of functionally specialized cell populations that interact with each other in a spatially and temporally coherent fashion. By means of neurochemical processes, these networks shape physiological and pathological behaviors as well as their

own functional and structural composition (Haider and McCormick, 2009). While the connection structure of the human brain is still incompletely understood quantitatively, broadly, a minimum of three hierarchical levels of network organization can be distinguished (Sporns et al., 2005). In addition to the level of individual cells (*microscale*), the level of local cellular assemblies (*mesoscale*), and the level of anatomically separated brain regions and their interconnecting fibers (*macroscale*) are differentiated; only the latter level is directly accessible by connectivity measures derived from non-invasive neuroimaging studies of the human brain.

The functional anatomy of these networks has a heritable component (Glahn et al., 2010), which is shaped by a multitude of genetic variants. Some of them confer risk for psychiatric disorders by affecting the functional integrity of regulatory circuits and controlling complex behavioral phenotypes such as cognitions and emotions (Meyer-Lindenberg, 2010a). In the past decade, technological advances in

* Corresponding author.

E-mail address: a.meyer-lindenberg@zi-mannheim.de (A. Meyer-Lindenberg).

neuroimaging and molecular genetics facilitated the implementation of a new research strategy (“*imaging genetics*”) that allows for the identification of the neurobiological effects of susceptibility genes (Meyer-Lindenberg and Weinberger, 2006; Pezawas and Meyer-Lindenberg, 2010). While initial studies focused on the examination of local brain characteristics, structural and functional connectivity measures have gained much popularity in the recent past, as they allow for a neural systems oriented view on the genetic risk architecture of psychiatric disease. Much of the enthusiasm in this field relates to the firm belief that, once the proximate neural intermediates of risk genes are identified, more efficient strategies for diagnosis and treatment can be discovered (Bray et al., 2010; Nickerson et al., 2000). This perspective is of utmost importance given the enormous burden that these conditions inflict on the affected individuals, their families, and the society in general.

This paper reviews the current knowledge derived from connectivity studies in psychiatric imaging genetics, ranging from simple correlative approaches to complex connectivity analyses based on graph theoretical metrics. In doing so, the article attempts to give an overview of the scientific methods and evidence that link these indices of neural network organization to healthy human behavior and the genetic susceptibility for mental illness. Naturally, due to the vast

amount of available data, this paper cannot provide a full representation of the imaging genetics literature on brain connectivity. Instead, by reporting selected empirical studies, an illustrative reflection of the current status quo is intended. In doing so, we highlight recent influential imaging genetics work related to the effects of psychiatric risk variants on brain connectivity measures in cognitive and emotion processing networks.

Imaging genetics: principles, challenges, and historical milestones

While it has long been recognized that a major risk factor for mental illness is genetic, the identification of causal genetic variants has remained difficult until recently. Notably, genetic susceptibility effects are not directly expressed at the behavioral level. Instead, gene effects are mediated by molecular and cellular mechanisms, which in turn modulate behavioral phenotypes by affecting the structural and functional properties of neural circuits (Fig. 1).

Principles and challenges

Several obstacles have complicated the identification of the intermediate neural mechanisms of psychiatric disease. First, while the

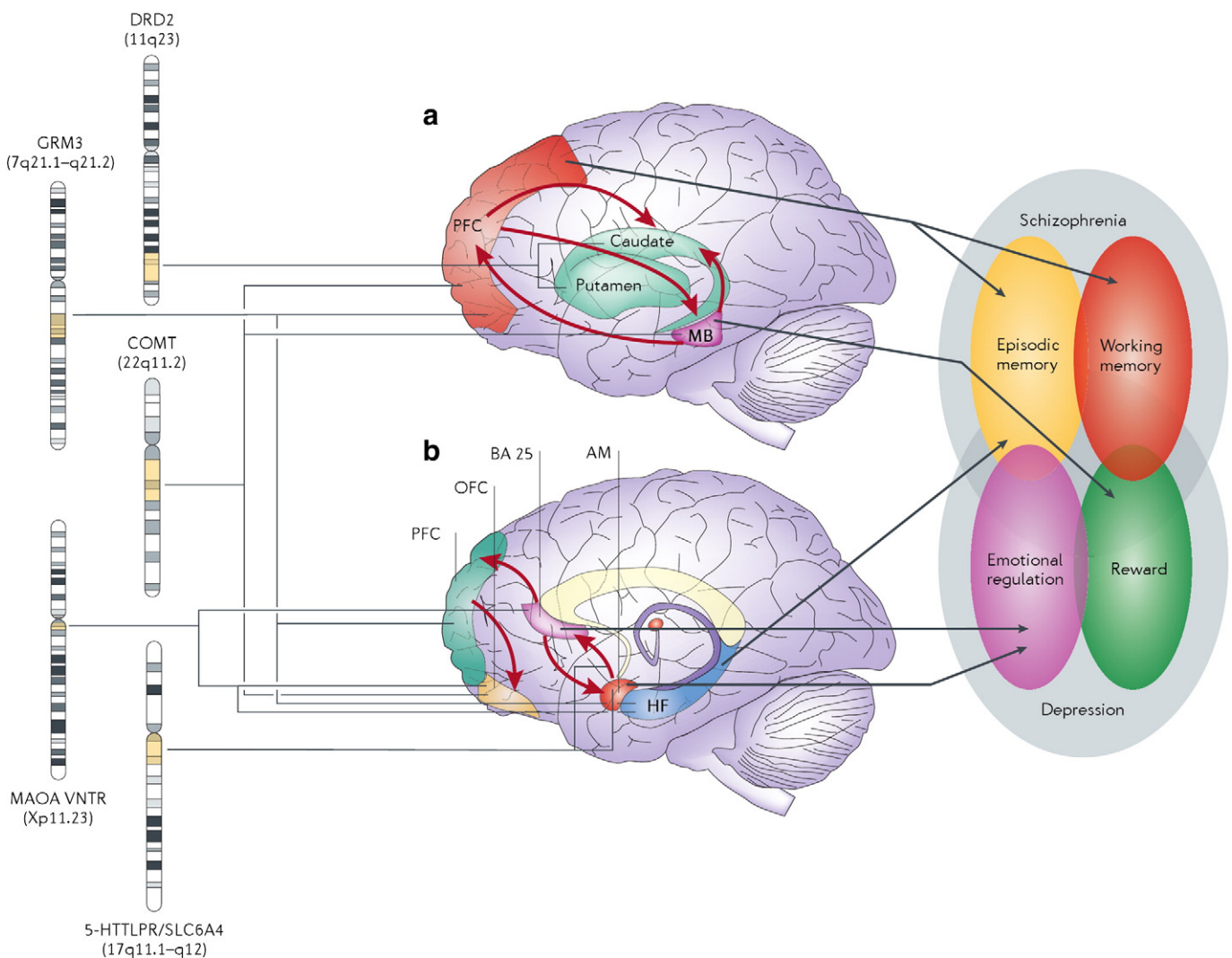


Fig. 1. The complex path from genes to behavior and disease phenotype: mediation through brain circuitry. Multiple genetic risk variants affect, through interaction with each other and the environment, multiple neural systems linked to several neuropsychological and behavioral domains that are impaired, in differing proportions, in psychiatric diseases. These circuits, in turn, are shown to mediate risk for schizophrenia and depression and various neuropsychological functions. Abbreviations: BA 25 = Brodmann's area 25, HF = hippocampal formation, OFC = orbitofrontal cortex. Graphic reprinted with permission from (Meyer-Lindenberg and Weinberger, 2006).

Download English Version:

<https://daneshyari.com/en/article/3072026>

Download Persian Version:

<https://daneshyari.com/article/3072026>

[Daneshyari.com](https://daneshyari.com)